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(54) Title: ANTI-ANGIOGENIC GENE THERAPY VECTORS AND THEIR USE IN TREATING ANGIOGENESIS-RELATED DISEASES		
(57) Abstract A method for inhibiting tumor growth in a human patient harboring a solid tumor, said method comprising administering to said patient a nucleic acid molecule which expresses in said patient an anti-angiogenic polypeptide selected from the group consisting of human angiostatin, murine angiostatin, human endostatin, murine endostatin, and angiogenesis-inhibiting fragments thereof, wherein expression of the anti-angiogenic polypeptide in the patient inhibits angiogenesis in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells, thereby inhibiting its growth.		

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ANTI-ANGIOGENIC GENE THERAPY VECTORS AND
THEIR USE IN TREATING ANGIOGENESIS-RELATED DISEASES

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Field of the Invention

This invention relates generally to gene therapy for, e.g., cancer.

Background of the Invention

Angiogenesis is the process by which new capillaries are formed from existing vasculature. It is a complex process which involves proliferation and migration of endothelial cells. It plays a fundamental role in reproduction, development and wound repair. Unregulated angiogenesis, however, can further the progression of many diseases, including tumor growth and metastasis, arthritis, diabetes, and some forms of blindness. For example, there is experimental evidence that limits of tumor size and growth are not the failure of the tumor cells to proliferate, but rather a failure of the tumor to provide sufficient nutrients and waste removal to its constituent cells by recruiting surrounding vasculature.

Summary of the Invention

The invention features a method for inhibiting tumor growth in a human patient harboring a solid tumor, involving administering to the patient a nucleic acid molecule which expresses in the patient an anti-angiogenic polypeptide selected from the group consisting of human angiostatin, murine angiostatin, human endostatin, murine endostatin, and angiogenesis-inhibiting fragments thereof, wherein expression of the anti-angiogenic polypeptide in the patient inhibits angiogenesis in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells, thereby inhibiting its growth.

In a second, related aspect, the invention features tumor inhibition, of

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the type just described, using nucleic acids molecules of the formula A-B, where A and B are polypeptide and/or export signal joined by a peptide bond; peptide A contains at least 100 amino acids and includes at least kringles 1, 2, and 3 of human or murine angiostatin; and peptide B contains at least 100
5 amino acids and includes at least 75% of the amino acid sequence of human or murine endostatin. Expression of the fusion anti-angiogenic polypeptide in the patient inhibits angiogenesis in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells, thereby inhibiting its growth. In some embodiments
10 of this hybrid polypeptide and/or export signal method, polypeptide and/or export signal A further includes kringle region 4 of angiostatin, and can also include kringle region 5 of plasminogen (the larger protein molecule of which angiostatin is a portion).

In both aspects of the invention, the nucleic acid molecule preferably
15 constitutes a portion of a viral vector or a plasmid, which can either be administered to the patient so that cells of the patient in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells are infected or transfected with the nucleic acid encoding the angiogenesis-inhibiting
20 polypeptide, or cells (of the patient, or another human donor, or an animal) are infected or transfected *ex-vivo*, and those infected or transfected cells are then infused into the patient so that the anti-angiogenic polypeptide is expressed in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells.

25 As will be discussed in more detail below, in particularly effective embodiments, the nucleic acid molecule includes a nucleotide sequence

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encoding a preactivation polypeptide and/or export signal for effecting Golgi and/or endoplasmic reticulum export of the anti-angiogenic polypeptide.

In another aspect, the invention features a method for treating a human patient suffering from diabetic retinopathy, involving administering to the patient one of the nucleic acid molecules described above.

The above and other features, objects and advantages of the present invention will be better understood by a reading of the following specification in conjunction with the drawings.

Brief Description of the Drawings

Fig. 1 depicts the structural relationship of angiostatin with plasminogen.

Fig. 2 depicts the structural relationship of endostatin with collagen type XVIII.

Fig. 3 depicts various viral (A. MSCV, murine retrovirus; B. Adeno-associated virus; C. HIV based retrovirus; E. recombinant adeno-virus) and non-viral (D. plasmid) vectors used in the construction of gene therapy vectors for this invention.

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MSCV: Murine Stem Cell Virus
 LTR: Long Terminal Repeat
 RSV: Rous Sarcoma Virus
 ITR: Inverted Terminal Repeat
 HTV: Human Immunodeficiency Virus
 IRES: Internal Ribosomal Entry Site
 GFP: Green Fluorescence Protein
 HBPRE: Hepatitis B Export Element
 RRE: Rev Response Element
 polyA: polyadenylation site
 ψ +: , , viral packaging sequence

The inverted triangle shows the site at which the anti-angiogenic constructs will be inserted using engineered MluI and XhoI restriction sites.

* denotes specific mutations within the long terminal repeat and leader which bestows the ability for expression in embryonic stem and hematopoietic stem cells.

The arrow denotes the direction of transcription.

Fig. 4 depicts in the left (A) panel nude mice which were implanted with human neuroblastoma cells (line SK-N-AS) transduced with a mock virus and in the right (B) panel, nude mice which were transplanted with human neuroblastoma cells transduced with a retroviral gene therapy vector encoding an angiostatin-endostatin fusion protein.

Fig. 5 shows the nucleotide sequence (SEQ ID NO: 1) and amino

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acid sequence (SEQ ID NO: 2) of human plasminogen and the nucleotide sequence (SEQ ID NO: 5) and amino acid sequence (SEQ ID NO: 6) of human angiostatin.

Fig. 6 shows the nucleotide sequence (SEQ ID NO: 9) and amino acid sequence (SEQ ID NO: 10) of murine endostatin.

Fig. 7 shows the nucleotide sequence (SEQ ID NO: 3) and amino acid sequence (SEQ ID NO: 4) of murine plasminogen and the nucleotide (SEQ ID NO: 7) and amino acid sequence (SEQ ID NO: 8) of murine angiostatin.

Detailed Description

10 This invention provides gene therapy using a vector having a nucleotide sequence encoding one of the above-identified anti-angiogenic polypeptides. Described below in more detail are some of the components of the vectors and methods of the invention.

By a gene therapy vector is meant a vector useful for gene therapy.

15 Gene therapy vectors carry a gene of interest that is useful for gene therapy.

The gene therapy vectors are able to be transferred to the cells of an animal, e.g., a human, and are able to express the gene of interest in such cells so as to effect gene therapy. The vector can be, e.g., chromosomal, non-chromosomal, or synthetic, and can be RNA or DNA. The vector can be, e.g., a plasmid, a

20 virus or a phage. Preferred vectors include, e.g., retroviral vectors, adenoviral vectors, adeno-associated vectors, herpes virus vectors, Simliki Forest Virus-based vector, Human Immunodeficiency virus, Simian Immunodeficiency virus, and non-viral plasmids. A preferred retroviral vector is Murine Stem Cell Virus (MSCV), which is a variant of Moloney Murine Leukemia Virus
25 (MoMLV).

By anti-angiogenic polypeptide is meant a polypeptide which inhibits

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angiogenesis. The terms polypeptide, protein and polypeptide and/or export signal are used interchangeably herein. By angiogenesis is meant the process by which new vasculature, in particular, new capillaries, are formed from existing vasculature. Angiogenesis is a complex process entailing numerous steps, including local dissolution of the basement membrane, migration of endothelial cells into the surrounding stroma, proliferation of the endothelial cells at the leading edge to form a migrating column of cells, branching and fusion of the newly formed vascular loops, and formation of a new basement membrane. By inhibiting angiogenesis is meant completely or partially inhibiting the formation of such new vasculature.

In certain embodiments, the anti-angiogenic polypeptide is an anti-angiogenic fragment of plasminogen (in particular, angiostatin), an anti-angiogenic fragment of collagen XVIII (endostatin) or a fusion of the two fragments.

Angiostatin is an internal fragment of plasminogen having a molecular weight of 38 or 45 kDa, depending on whether it contains kringles 1-3 or 1-4. In the invention, either can be used, or a molecule including kringles 1-3 and a portion of kringle 4 can be used. Angiostatin can be naturally produced in vivo in small amounts by tumor cells, e.g. murine Lewis lung carcinoma cells, by proteolytic cleavage of plasminogen so as to eliminate the N-terminal portion including the signal polypeptide and/or export signal and the preactivation polypeptide and/or export signal, as well as the C-terminal portion following kringle 3 or 4. Mouse and human angiostatin have been purified and sequenced. In preferred embodiments, the gene therapy vectors of this invention encode angiostatin having kringles 1, 2 and 3, or angiostatin having kringles 1, 2, 3 and 4.

In another preferred embodiment, the anti-angiogenic polypeptide is

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endostatin or a biologically active analog or fragment thereof. Endostatin can be naturally produced *in vivo* in small amounts by tumor cells, e.g., murine angiosarcoma cells, by proteolytic cleavage of endogenous collagen XVIII so as to eliminate the N-terminal portion including the signal polypeptide and/or export signal and the preactivation polypeptide and/or export signal, as well as the C-terminal portion following kringle 3 or 4. See Fig. 2. Mouse endostatin has been sequenced, and the human molecule (SEQ ID NOs: 17 and 18) forms a portion of collagen 18 (SEQ ID NOs: 19 and 20).

The human molecule position and sequence are apparent from an alignment of the active, Lys-terminated active region of human collagen 18 with murine endostatin, such that the C-terminal lysine residues align, bringing the active endostatin sequences into alignment.

In yet another preferred embodiment, the anti-angiogenic polypeptide is an in-frame fusion of angiostatin or a biologically active analog or fragment thereof and endostatin or a biologically active analog or fragment thereof. Preferably, the angiostatin or biologically active analog or fragment is 5' of the endostatin or biologically active analog or fragment. In certain embodiments, the angiostatin-endostatin fusion proteins exhibit synergistic anti-angiogenic properties.

By fragment is meant some portion of the naturally occurring anti-angiogenic polypeptide. Preferably, the fragment is at least 20 amino acid residues, more preferably at least 50 amino acid residues, and most preferably at least 100 amino acid residues in length. Fragments include chimeric constructs composed of at least a portion of the relevant gene and another molecule. The ability of a candidate fragment to exhibit a biological activity of the anti-angiogenic polypeptide can be assessed by methods known to those skilled in the art, e.g., by its ability to inhibit proliferation of bovine capillary

cells, or by its ability to inhibit growth of primary tumor cells, e.g., as described herein. See, e.g., Example 9. Also included are fragments containing residues that are not required for biological activity of the fragment or that result from alternative mRNA splicing or alternative protein processing events.

5 Internal or terminal fragments of a polypeptide can be generated by removing one or more nucleotides from one end (for a terminal fragment) or both ends (for an internal fragment) of a nucleic acid which encodes the polypeptide.

10 In preferred embodiments, the gene therapy vector of this invention is capable of hybridizing to the native anti-angiogenesis polypeptide-encoding regions and has at least about 80%, preferably at least about 90%, and more preferably at least about 95%, sequence identity to the native nucleotide sequences, and encodes a polypeptide which has anti-angiogenic activity; or a biologically active fragment of any of the above nucleotide sequences wherein
15 the encoded polypeptide has anti-angiogenic activity.

 The nucleotide sequences of the present invention can be in the form of RNA or DNA, and the nucleotide sequence can be double-stranded or single stranded and, if single stranded, can be the coding strand or non-coding (anti-sense) strand.

20 The coding sequence which encodes the anti-angiogenic polypeptide can be identical to the native coding sequences, or can be a different coding sequence which, as a result of the degeneracy of the genetic code, encodes the same anti-angiogenic polypeptide.

 In certain embodiments, the gene therapy vector also has a nucleotide
25 sequence encoding a signal polypeptide and/or export signal (SP) for effecting secretion of the anti-angiogenic polypeptide. Examples of signal polypeptide and/or export signal include plasminogen signal polypeptide and/or export

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signal. Preferably, the signal polypeptide and/or export signal is 5' (i.e., upstream) of the nucleotide sequence encoding the anti-angiogenic polypeptide.

Preferably, the gene therapy vector has a nucleotide sequence encoding a preactivation polypeptide and/or export signal (PAP), which is a small polypeptide and/or export signal which effects folding and secretion of the anti-angiogenic polypeptide *in vivo*. Examples of preactivation polypeptide and/or export signal include plasminogen preactivation polypeptide and/or export signal, described herein, and PAP's of other proteins in the blood clotting cascade.

Preferably, the preactivation polypeptide and/or export signal is positioned 5' of the nucleotide sequence encoding the anti-angiogenic polypeptide. In embodiments which have a signal sequence and an anti-angiogenic polypeptide, preferably the preactivation polypeptide and/or export signal is 5' of the nucleotide sequence encoding the anti-angiogenic polypeptide, and 3' of the nucleotide sequence encoding the signal polypeptide and/or export signal.

We have discovered that results obtained using constructs containing a PAP-encoding nucleic acid sequence are far superior to results using constructs lacking a PAP-encoding sequence. Our hypothesis to explain these unexpectedly superior results with PAP is that, during the complex process by which the anti-angiogenic polypeptide is expressed and processed in living cells, the PAP polypeptide and/or export signal facilitates the export of the polypeptide from the cellular Golgi apparatus and/or the endoplasmic reticulum (ER). The corollary is that, absent PAP, a significant portion of the expressed polypeptide remains trapped in the Golgi and/or ER.

The PAP exemplified herein is derived from human plasminogen; this

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PAP is currently preferred. Our discovery that the use of a PAP dramatically improves results leads us to believe that other PAP's would be useful as well, and such others are therefore contemplated for use in the invention. Thus, as used herein, "PAP" refers to a polypeptide and/or export signal which is

5 naturally associated with a eukaryotic (preferably human) protein, the exportation of which is facilitated by its associated PAP. Examples of other human proteins whose Golgi/ER export is PAP-facilitated include other secreted proteins of the blood coagulation cascade, e.g., fibrinogen, prothrombin, Factor VIII, and Factor IX. Other secreted human proteins also
10 are associated with potentially useful PAPs.

It is not essential that the PAP used in the invention be identical in amino acid sequences to a native PAP; it is well-known that polypeptide and/or export signal that facilitate protein secretion or export, e.g., signal polypeptide and/or export signal and PAPs, can vary from the native forms to a certain
15 extent and still retain their function. Therefore, PAPs useful according to the invention preferably have 75% or greater amino acid sequence identity with a native PAP.

In certain embodiments, the gene therapy vector has a nucleotide sequence encoding a tag for identification of the anti-angiogenic polypeptide and/or export signal. In certain embodiments, the tag is 5' of the nucleotide
20 sequence encoding the anti-angiogenic polypeptide; in other embodiments, the tag is 3' of the nucleotide sequence encoding the anti-angiogenic polypeptide. In embodiments in which the anti-angiogenic polypeptide is endostatin or an angiostatin-endostatin fusion, it is preferred that the tag be 5' of the nucleotide
25 sequence encoding endostatin.

In certain embodiments the gene therapy vector includes a selectable

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marker, e.g., a Neomycin phosphotransferase gene, or a humanized red-shifted green fluorescent protein.

The invention also includes a cell infected or transfected with a gene therapy vector described herein. Preferably, the cell is an animal cell, more preferably an autologous or allogeneic human cell. The gene therapy vectors described herein can be introduced into a cell, e.g., by transformation, transfection, transduction, infection, or ex vivo injection. They can be targeted to a particular cell type.

Administration of nucleic acid, e.g., a gene therapy vector, can be accomplished by any method which allows the nucleic acid to reach the target cells. These methods include, e.g., injection, deposition, implantation, suppositories, oral ingestion, inhalation, topical administration, or any other method of administration where access to the target cells by the nucleic acid is achieved. Injections can be, e.g., intravenous, intradermal, subcutaneous, intramuscular or intraperitoneal. Implantation includes inserting implantable drug delivery systems, e.g., microspheres, hydrogels, polymeric reservoirs, cholesterol matrices, polymeric systems, e.g., matrix erosion and/or diffusion systems and non-polymeric systems, e.g., compressed, fused or partially fused pellets. Suppositories include glycerin suppositories. Oral ingestion doses can be enterically coated. Inhalation includes administering the nucleic acid with an aerosol in an inhalator, either alone or attached to a carrier that can be absorbed.

In certain embodiments of the invention, administration can be designed so as to result in sequential exposures to the nucleic acid over some time period, e.g., hours, days, weeks, months or years. This can be accomplished by repeated administrations of the nucleic acid, e.g., by one of the methods described above, or alternatively, by a controlled release delivery system in

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which the nucleic acid is delivered to the animal over a prolonged period without repeated administrations. By a controlled release delivery system is meant that total release of the nucleic acid does not occur immediately upon administration, but rather is delayed for some time. Release can occur in bursts or it can occur gradually and continuously. Administration of such a system can be, e.g., by long acting oral dosage forms, bolus injections, transdermal patches or subcutaneous implants. Examples of systems in which release occurs in bursts include, e.g., systems in which the nucleic acid is entrapped in liposomes which are encapsulated in a polymer matrix, the liposomes being sensitive to a specific stimulus, e.g., temperature, pH, light, magnetic field, or a degrading enzyme, and systems in which the nucleic acid agent is encapsulated by an ionically-coated microcapsule with a microcapsule core-degrading enzyme. Examples of systems in which release of the nucleic acid is gradual and continuous include, e.g., erosional systems in which the nucleic acid is contained in a form within a matrix, and diffusional systems in which the nucleic acid permeates at a controlled rate, e.g., through a polymer. Such sustained release systems can be, e.g., in the form of pellets or capsules.

The nucleic acid is administered to the patient in a therapeutically effective amount. By therapeutically effective amount is meant that amount which is capable of at least partially preventing or reversing the disease. A therapeutically effective amount can be determined on an individual basis and will be based, at least in part, on consideration of the patient's size, age, the efficacy of the particular nucleic acid used, the type of delivery system used, the time of administration relative to the onset of disease symptoms, and whether a single, multiple, or controlled release dose regimen is employed. A therapeutically effective amount can be determined by one of ordinary skill in the art employing such factors and using no more than routine experimentation.

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In certain embodiments, a therapeutically effective amount of an anti-angiogenic polypeptide is administered by providing to the animal a nucleic acid encoding the polypeptide and expressing the polypeptide in vivo. Nucleic acids encoding the polypeptide, or mutants thereof, can be administered in any biologically effective carrier, e.g. any formulation or composition capable of effectively delivering the nucleotide sequence for the anti-angiogenic polypeptide to cells in vivo. Approaches include, e.g., insertion of the nucleic acid into viral vectors. Viral vectors can be delivered to the cells, e.g., by infection or transduction using the virus. Viral vectors can also be delivered to the cells, e.g., by physical means, e.g., by electroporation, lipids, cationic lipids, liposomes, DNA gun, $\text{Ca}_3(\text{PO}_4)_2$ precipitation, or delivery of naked DNA. In certain preferred embodiments, the virus is administered by injection, e.g., intramuscular injection, in a dose range of about 10^3 to about 10^{10} infectious particles per injection, more preferably in a dose range of about 10^5 to about 10^8 infectious particles per injection. Single or multiple doses can be administered over a given period of time, depending, e.g., upon the disease.

An alternative is insertion of the nucleic acid encoding the anti-angiogenic polypeptide into a bacterial or eukaryotic plasmid. Plasmid DNA can be delivered to cells with the help of, e.g., cationic liposomes (lipofectin™, Life Technologies, Inc., Gaithersburg, MD) or derivatized (e.g., antibody conjugated), polylysine conjugates, gramicidin S, artificial viral envelopes or other such intracellular carriers, as well as direct injection of the gene construct or $\text{Ca}_3(\text{PO}_4)_2$ precipitation carried out in vivo, or by use of a gene gun. The above-described methods are known to those skilled in the art and can be performed without undue experimentation.

Since transfer of the nucleic acid to appropriate target cells represents the critical first step in gene therapy, choice of the particular gene delivery

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system will depend on such factors as the intended target and the route of administration, e.g., locally or systemically. Targets for delivery of the nucleic acid can be, e.g., specific target cells which are diseased. For example, the target can be, e.g., the peritoneal cavity, gastro-intestinal tract, bone marrow cavity, liver, lungs, muscles, vasculature, pericardial cavity, pleural cavity, skin, sub-cutaneous or deep connective tissues, central nervous system, spinal fluid, eye, or specific sites of tumor growth. Administration can be directed to one or more cell types, and to one or more cells within a cell type, so as to be therapeutically effective, by methods known to those skilled in the art. For example, the nucleic acid can be, e.g., coupled to an antibody, to a ligand to a cell surface receptor, or to a toxin component, or can be contained in a particle which is selectively internalized into cells, e.g., liposomes, or a virus where the viral receptor binds specifically to a certain cell type, or a viral particle lacking the viral nucleic acid, or can be administered by local injection.

In certain embodiments, the nucleic acid is administered to the patient by introducing *ex vivo* the nucleic acid into cells of the patient, or into syngeneic or allogeneic or xenogeneic cells, and then administering the cells having the nucleic acid to the animal. Any cell type can be used. In certain embodiments, the cells having the introduced nucleic acid are expanded and/or selected after the nucleic acid transfer. The cells having the transferred nucleic acid are subsequently administered to the patient. Preferably, the cells are administered in a dose range of about 1×10^6 to about 1×10^9 cells/dosage/day, and most preferably at about 1×10^7 to about 1×10^8 cells/dosage/day. The cells can be administered by any method which results in delivering the transferred nucleic acid in the cells to the desired target. For example, the cells can be implanted directly into a specific tissue of the patient, or implanted after encapsulation within an artificial polymer matrix. Examples of sites of

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implantation include, e.g., the peritoneal cavity, gastro-intestinal tract, bone marrow cavity, liver, lungs, muscles, vasculature, pericardial cavity, pleural cavity, skin, sub-cutaneous or deep connective tissues, central nervous system, spinal fluid, eye, or specific sites of tumor growth.

5 Systemic delivery can be achieved, e.g., by introducing the nucleic acid into cells which circulate in the peripheral blood of the patient, or which give rise to cells which circulate in the peripheral blood. In certain embodiments, the nucleic acid is introduced into such cells *ex vivo*, and these cells are then administered to the patient, resulting in systemic delivery within the peripheral
10 blood. These cells can be the cells of the patient or allogeneic cells. Preferred cells in which the nucleic acid can be introduced are hematopoietic cells.

 In certain embodiments, other therapy is additionally administered. For example, if the animal is being treated for a tumor, other tumor therapy, e.g., another therapeutic agent, chemotherapy, radiation or surgery, is additionally
15 administered to the patient, either simultaneously or at different times.

 Treating is meant to include, e.g., preventing, treating, reducing the symptoms of, or curing the disease. I.e. treating a tumor includes preventing growth of the tumor, causing shrinkage of the tumor, or preventing development of micro-metastases.

20 Preferably, the recombinant nucleic acid is a gene therapy vector, e.g., as described herein. Preferably, the anti-angiogenic polypeptide is angiostatin, endostatin, an angiostatin-endostatin fusion protein, or biologically active analogs or fragments thereof. In certain embodiments, the angiostatin has kringles 1, 2 and 3; in other embodiments, the angiostatin has kringles 1, 2, 3
25 and 4, and, in some embodiments, kringle 5 of human or murine plasminogen. Angiostatin is described in O'Reilly and Folkman U.S. Patent No. 5,639,725, hereby incorporated by reference. Endostatin is described in O'Reilly and

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Folkman PCT Appln. No. WO 97/15666, published May 1, 1997, hereby incorporated by reference.

In certain embodiments, the recombinant nucleic acid has been introduced *ex vivo* into cells so as to express the anti-angiogenic polypeptide in the cells, and the recombinant nucleic acid is administered to the patient by administering to the patient the cells containing the recombinant nucleic acid. In certain embodiments, the cells are derived from the patient; in other embodiments the cells are allogeneic cells relative to the cells of the patient.

Where cells are infected or transfected *ex vivo* for later infusion into the patient, the cells are preferably hematopoietic cells, but can also be mesenchymal cells, stem cells, epithelial cells (e.g., from the gut), or dendritic cells.

The gene therapy vectors of the invention can be provided in a pharmaceutical composition comprising a therapeutically effective amount of the recombinant nucleic acid together with a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers include, e.g., water, saline, dextrose, glycerol, ethanol, liposomes and lipid emulsions.

The following non-limiting examples further illustrate the present invention.

EXAMPLES

Example 1: Construction of Inserts for Gene Therapy Vectors Containing cDNA for Angiostatin, Endostatin or Angiostatin-Endostatin Fusion Proteins

The following genetic constructs are inserted into retroviral gene therapy vectors; the genetic constructs contain human or murine cDNA for angiostatin, endostatin or an angiostatin-endostatin fusion, and DNA encoding a signal

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polypeptide and/or export signal (SP); a tag (FLAG); and, preferably, a preactivation polypeptide and/or export signal (PAP). The constructs are all made using standard genetic engineering techniques, and their insertion into retroviral gene therapy vectors is carried out using known methods. The

5 constructs have the following components:

Murine Constructs

SP-K1-K2-K3-Flag

SP-K1-K2-K3-K4-Flag

SP-K1-K2-K3-K4-K5-Flag

10 SP-PAP-K1-K2-K3-Flag

SP-PAP-K1-K2-K3-K4-Flag (SEQ ID NO: 11 and 12)

SP-Flag-Endo (SEQ ID NO: 13 and 14)

SP-K1-K2-K3-Flag-Endo

SP-K1-K2-K3-K4-Flag-Endo (SEQ ID NO: 15 and 16)

15 SP-PAP-K1-K2-K3-Flag-Endo

Human Constructs

SP-K1-K2-K3

SP-K1-K2-K3-K4

SP-K1-K2-K3-K4-K5

20 SP-PAP-K1-K2-K3

SP-PAP-K1-K2-K3-K4

SP-PAP-K1-K2-K3-K4-K5

SP-Endo

SP-K1-K2-K3-Endo

25 SP-PAP-K1-K2-K3-Endo

Nucleic acid and amino acid sequences for mouse and human angiostatin and endostatin used in these constructs are shown in Figs. 5-7.

Nucleic acid and amino acid sequence of the FLAG peptide:

amino terminus-	ASP	TYR	LYS	ASP	ASP	ASP	ASP	LYS
5'-	GAC	TAC	AAG	GAC	GAC	GAT	GAC	AAG

Human plasminogen derivative constructs

The entire coding region of the human plasminogen cDNA from the start (ATG) to the stop (TAA) codon is 2433bp in size.

This sequence encodes a signal peptide (bp 1-57), a preactivation peptide (bp 58-288), and 5 distinct structural regions known as kringles (K1-K3 from bp 289-1092; K4 from bp 1093-1380; K5 from bp 1381-1740). Please note that although I have given precise bp measurements for kringles K4 and K5, it can be argued that the sequence encoding K4 is between bp 1056-1440 and the sequence encoding K5 is between bp 1362-1680.

A DNA fragment encoding a portion of the human plasminogen protein from bp 1 to 1377 was obtained by PCR of a widely available human liver cDNA library using synthetic DNA oligonucleotides complementary to sequences immediately preceding the signal peptide and immediately following kringle 4. This fragment contains the signal peptide (bp 1-57), the preactivation peptide (bp 58-288), kringles 1 (bp 289-549), 2 (bp 550-804), 3 (bp 805-1092) and 4 (bp 1093-1380). The synthetic oligonucleotides used for this reaction contained engineered recognition sites for the restriction enzymes EcoRI and XhoI. Following the PCR reaction the amplified fragment was cloned into the EcoRI/XhoI sites of BluescriptSK(-) (Stratgene) using standard techniques (Maniatis). Following cloning the integrity of the amplified sequence was verified by sequencing both strands using the Sanger method (Sanger). Various derivatives of the cloned fragment were subsequently constructed using BluescriptSK(-) (Stratgene) as a backbone. A full list of the derivatives are described in Table 1. Briefly, the variations are composed of constructs containing various combinations of kringles with or without the signal and/or preactivation peptide sequences. These derivatives were constructed using both standard techniques as well as PCR and the use of double stranded synthetic oligonucleotides. In all cases the integrity of the start codon, coding sequence and termination codon was verified by double stranded sequencing using the Sanger method.

Murine plasminogen derivative constructs

The coding sequence for murine plasminogen is 2439bp in size and, similar to the human plasminogen cDNA encompasses a sequence encoding signal and preactivation peptides (bp 1-57 and 58-288 respectively) in addition to 5 kringle regions; kringle 1-3 (bp 289-1092), kringle 4 (bp 1093-1380) and kringle 5 (bp 1381-1743). Again, although I have given precise bp measurements for kringles K4 and K5, it can be argued that the sequence encoding K4 is between bp 1056-1440 and the sequence encoding K5 is between bp 1362-1680.

The murine plasminogen cDNA has previously been cloned and was made available to us. Derivatives of murine plasminogen were constructed using sequences derived from bp 1-1743 of the coding sequence. Various combinations of kringle regions with or without signal and preactivation peptide regions were made using BluescriptSK(-) (Stratgene, La Jolla, CA) as the vector backbone. These derivatives were constructed using standard cloning techniques (Maniatis, Molecular cloning; a laboratory manual, second edition, 1989) in combination with PCR utilizing synthetic oligonucleotides using

Angiostatin function was not altered by adding the FLAG polypeptide and/or export signal to either the N- or C-terminal ends, whereas endostatin was functional only if FLAG was added to its N-terminal end.

Example 2: Construction of Retroviral Gene Therapy Vectors

5 This example illustrates the construction of retroviral gene therapy vectors comprising cDNA for angiostatin, endostatin or angiostatin-endostatin fusion proteins.

The DNA inserts from Example 1 were inserted into two retroviral vectors. Both vectors were derived from the Murine Stem Cell Virus (MSCV),
10 which is a variant of Moloney Murine Leukemia Virus (MoMLV) having several mutations allowing high, sustained expression in hematopoietic stem cells and their progeny. In both cases, the angiostatin, endostatin, or angiostatin-endostatin fusion DNA inserts were under the transcriptional control of the retroviral left Long Terminal Repeat (LTR). In the first vector,
15 the dominant selectable marker was the Neomycin phosphotransferase gene (NeoR), which confers resistance to G418, and is driven by an internal phosphoglycerate kinase (PGK) promoter. In the second vector, the dominant selectable marker was the humanized, red-shifted green fluorescent protein (EGFP), which is co-translationally expressed by means of an Internal
20 Ribosome Entry Site (IRES) from the Encephalomyocarditis virus (EMCV).

The retroviral gene therapy vectors were transfected by CaPO_4 precipitation in the transient ecotropic packaging cell-line BOSC 23, Pear et al., *PNAS* 90:8392 (1993). Viral supernatants were collected two days thereafter and filtered through 0.45 mm filters. Filtered viral supernatants were
25 subsequently used to infect GENETIX's stable amphotropic retroviral packaging cell-line AM12 (Genetix Pharmaceuticals, Inc., Cambridge, MA). After another two days, viral supernatants from transduced AM12 were filtered

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and used to infect GENETIX's stable ecotropic retroviral packaging cell-line GP+E86 (Genetix Pharmaceuticals, Inc.). Both transduced AM12 and GP+E86 were then selected in the presence of G418 (in the case of constructs bearing NeoR) or sorted by Fluorescent Activated Cell Sorter (FACS) for EGFP expression. Viral titers were estimated according to standard practice by counting G418 resistant colonies among NIH3T3 cells exposed to diluted virus preparation. Ecotropic viral titers were above 5×10^5 /ml of viral supernatants, only 3-fold lower than "empty" control vectors. No Replication Competent Retrovirus (RCR) was detected in standard assays.

10 Example 3: Transduction of Target Cells Using Retroviral Gene Therapy Vectors

This example illustrates the stability of retroviral gene therapy vector transmission and the lack of toxicity in non-endothelial target cells.

Following 24-hour incubation of confluent viral producer cells in 100 mm plates, viral supernatant was removed and filtered (0.45 μ m filter, Gelman Sciences, Ann Arbor, MI). Viral supernatant, containing 7 μ g/ml polybrene (Sigma, St. Louis, MO), was added to target cells 24 hours after plating the target cells. Fresh medium was added after 4-12 hours, and, after an additional 48 hours, cells were selected for retroviral infection by exposure to medium containing 1 mg/ml G418 (Gibco BRL, Grand Island, NY) or by FACS sorting (FACStar cell sorter, Becton Dickinson, San Jose, CA). The stability of transmission of the retroviral gene therapy vectors described in Example 2 was examined by Southern blot analysis of transduced NIH3T3 cells, using specific probes (EGFP) and restriction enzyme digestion of genomic DNA with SacI, which cuts only once in each LTR. Stable chromosomal integration of intact proviruses of appropriate length was observed with all constructs.

The lack of non-specific toxicity on non-endothelial cells was

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established by using filtered viral supernatants to transduce various tumor cell-types and cell-lines (NIH3T3 cells, K562 cells (ATCC), and human SK-N-AS neuroblastoma cells; Cohen, P.S., *Cancer Research*, 55:2380 (1995). Transduced cell populations were subsequently selected with G418 or sorted for EGFP expression by FACS. No obvious effects on cell viability, growth or other phenotypical characteristics were detected.

Example 4: Protein Expression of Angiostatin, Endostatin and Angiostatin-Endostatin Fusion Proteins in Cells Transduced with Retroviral Gene Therapy Vectors

This example illustrates that recombinant angiostatin, endostatin, and angiostatin-endostatin fusion proteins were readily detected in retrovirally transduced cells and their supernatant, indicating efficient expression and secretion.

MSCV virus based vectors containing sequences encoding murine Kringle 1 (K1), K1K5, K1K2K3, K1K2K3K4, and K1K2K3K4K5 were used to transduce NIH3T3 cells. With regard to the murine recombinant proteins, Western blot analysis of transduced cells and their supernatant was performed by means of a monoclonal antibody that recognizes the FLAG polypeptide and/or export signal. Because this antibody is not mono-specific, significant cross-reactivity with murine proteins was apparent. However, by comparing the pattern obtained with mock cells, it was clear that the antibody revealed an additional band of appropriate size in all transduced cells. Moreover, the recombinant proteins were detected in cell supernatants at levels above 50 ng/ml, using a protein concentration/semi-purification procedure (Centricon columns, Amicon, Beverly, MA). With regard to the human recombinant proteins, no FLAG tag was added, so a monoclonal antibody that recognizes specifically the first three kringles of human plasminogen in its native, non-

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denatured form was used; O'Reilly et al., *Cell* 79:315 (1994). Because of this constraint, Western blot analysis using denaturing gels could not be performed. An ELISA assay was performed which indicated that human recombinant angiostatin was detected at levels likely to be therapeutic according to previous findings in the model of Lewis Lung Carcinoma *Id*.

These results indicate that high levels of recombinant proteins of expected length were expressed in retrovirally transduced cells and were efficiently secreted.

Example 5: In Vivo Anti-Tumor Activity of Cells Transduced with Gene Therapy Vectors Encoding the Angiostatin-Endostatin Fusion Protein

Human SK-N-AS neuroblastoma cells (Cohen, 1995) were transduced with the retroviral gene therapy vector containing the angiostatin-endostatin fusion protein, described in Example 2. These cells (1,000,000) were suspended in 1 mL Dulbecco's phosphate buffered saline and injected into the right mid-quadrant of nude immuno-compromised mice. While no impairment of the *in vitro* growth of transduced cells was observed, a dramatic decrease in tumor growth in nude mice cells following subcutaneous implantation of the transduced cells was evident as compared to "mock virus"-transduced control cells.

Example 6: Ex Vivo Transfer of Retroviral Gene Therapy Vectors Encoding Anti-Angiogenic Polypeptides to Primary Hematopoietic Cells, and Subsequent Transplantation to Recipient Mice

This example illustrates infection of primary hematopoietic cells from

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donor mice with retroviral gene therapy vectors encoding angiostatin, endostatin, or an angiostatin-endostatin fusion protein, and a selectable GFP marker, and subsequent transplantation of the transduced hematopoietic cells into recipient mice.

5 Femoral bone marrow cells are harvested from male donor C57BL6/J-Ly5.1 mice (Jackson Labs, Bar Harbor, ME), intravenously injected four days previously with 150 mg/kg of 5-fluorouracil (5-FU). Bone marrow cells are cultured for two days in medium composed of DMEM, 15% fetal calf serum, 10 ng/ml human IL-6, 6 ng/ml murine IL-3 and 100 ng/ml murine Steel factor
10 prior to two days of culture atop a confluent monolayer of irradiated (1,500 cGy, ¹³⁷Cs γ-irradiation) viral producer cells in the above medium including 6 ug/ml of prolamine sulfate. The viral producer cells are transfected with a retroviral gene therapy vector, as described above. Upon completion of the co-culture infection protocol, recovered non-adherent cells are cultured for an
15 additional 48 hours to allow for expression of the transferred GFP gene. Retrovirally transduced cells expressing the transferred GFP gene are subsequently identified and selected for, using a FACStar+ cell sorter (Becton Dickinson, San Jose, CA). The GFP+ cells are intravenously injected into congenic female C57BL6/J-Ly5.2 recipient mice (National Cancer Institute,
20 Washington, DC) previously given 950 cGy (83cGy/min, ¹³⁷Cs γ-rays) of whole body irradiation. In each case, a small fraction of GFP+ sorted cells is used for day 12 CFU-S and *in vitro* clonogenic progenitor assays to assess the efficiency of the infection and selection procedures on these more mature cell types.

25 Example 7: Engraftment of Recipient Mice with Donor-Derived Hematopoietic Cells

This example illustrates engraftment of the recipient mice with the

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donor-derived transfected hematopoietic cells from Example 6.

The donor and recipient mice are phenotypically distinguishable on the basis of Y chromosome specific sequences, as well as on the basis of allelic differences at the murine CD45 cell surface antigen locus. Male donor mice are homozygous for the CD45.2 allele, while female recipient mice are homozygous for CD45.1. The engraftment of recipient mice with donor-derived (CD45.2+) cells is assessed at both short (5 weeks) and long (34 months) time points post-transplant by flow cytometric analysis of peripheral blood samples stained with a phycoerythrin labeled antibody specific for the CD45.2 antigen (Pharmingen, San Diego, CA). The results indicate that engraftment occurs.

Example 8: Proviral Marking and GFP Expression in Recipient Mice

This example illustrates the presence of recombinant provirus and expression of the transferred GFP gene in the recipient mice from Example 6.

The level of proviral marking in reconstituted animals is initially determined by Southern blot and semi-quantitative PCR analysis of DNA obtained from peripheral blood leukocytes. The large majority of donor-derived (CD45.2+) cells in recipient mice contain a minimum of one copy of recombinant provirus. In addition, flow cytometric analysis of peripheral blood leukocytes is performed to ascertain the proportion of cells expressing the transferred GFP cDNA. Because the GFP and angiogenic inhibitor protein cDNAs are both driven from the same regulatory sequences, due to the inclusion of an internal ribosomal entry site (IRES) element, the analysis of GFP expression in the peripheral blood provides an indirect measurement of the levels of anti-angiogenic protein being expressed. The results indicate expression of the transferred genes.

Example 9: Anti-Angiogenic Polypeptide Expression in Recipient Mice

This example illustrates the presence of anti-angiogenic polypeptide in the sera of the recipient mice from Example 6, using both physical and functional assays.

5 Serum obtained from the transplanted animals described in Example 6 is used for ELISA using an antibody specific for the synthetic FLAG epitope (IBI, Eastman Kodak, New Haven, CT) and compared against known standards of purified protein. Results indicate the presence of the anti-angiogenic polypeptide in the serum.

10 To determine whether a functional anti-angiogenesis polypeptide is present in the circulation, sera from transplanted animals is tested for its ability to inhibit the proliferation of bovine capillary cells *in vitro*; O'Reilly (1994).

Briefly, cells are plated in 24 well dishes at 25,000 cells/ml and maintained in DMEM with 5% bovine calf serum for 24 hours. The medium is then replaced

15 with fresh medium containing various dilutions of the test serum. After 20 minutes of incubation, fresh medium including b-FGF (final concentration 1 ng/ml) is added and the cells are cultured for 72 hours. Cells are then dispersed using trypsin and the cell number determined by Coulter counter. Results indicate that functional anti-angiogenic polypeptide is present in the sera of the

20 recipient mice.

In addition, the ability of circulating anti-angiogenic polypeptide to inhibit the growth of primary tumor cells is assessed. Transplanted mice are subcutaneously injected with one million Lewis lung carcinoma (LLC) cells (O'Reilly, (1994)) at the proximal midline of their dorsal skin. The mice are

25 closely monitored for survival, tumor size and growth, and overall health.

Results indicate that the anti-angiogenic polypeptides from the sera of the

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recipient mice inhibit growth of the LLC tumor cells.

Finally, upon sacrifice of the transplanted recipient mice, blood, spleen, thymus and bone marrow are harvested and analyzed for the presence of proviral DNA by Southern analysis as well as expression of the transferred GFP and anti-angiogenic polypeptide cDNAs by flow cytometry and ELISA. Moreover, a portion of bone marrow cells is re-transplanted into secondary recipients to generate individual day 12 spleen colonies, as well as plated in methylcellulose to assess in vitro clonogenic progenitors. Individual clones are analyzed for proviral DNA by PCR or Southern blot, and for gene expression by flow cytometry and ELISA. Results of these tests also indicate the presence of proviral DNA and expression of the anti-angiogenic polypeptides and marker proteins.

Example 10: Evaluating the Efficacy of Retroviral Gene Therapy Vectors Encoding Anti-Angiogenic Polypeptides on Various Human Cancers Implanted in SCID Mice Using Ex Vivo Gene Therapy

This example illustrates a method for rapidly screening various forms of human cancer to determine susceptibility to treatment by the systemic delivery of anti-angiogenic polypeptides.

The methods for gene transfer, assessment of proviral marking and assessment of transferred gene expression as described in Examples 3 through 9 are repeated using immuno-deficient SCID mice, with the following exceptions. Since SCID mice are more sensitive to γ -irradiation than C57BL6/J mice, the female SCID recipients receive a lower dose of 400cGy of whole body irradiation in contrast to the 950cGy required for C57BL6/J. In addition, since the SCID mice do not possess allelic differences at the CD45 cell surface antigen locus, donor and recipient cells are phenotypically distinguished on the basis of Y chromosome specific sequences using Southern

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blot analysis.

Bone marrow from male donor SCID mice is infected, selected for on the basis of expression of the transferred GFP marker cDNA, and transplanted into irradiated female SCID recipients. Engraftment with provirally marked cells and expression of the transferred genes is demonstrated. The mice are then separately implanted with a variety of human tumor cell types, e.g., breast adenocarcinoma, lung squamous cell carcinoma, and brain glioblastoma. In each case, the ability of the anti-angiogenic polypeptides to inhibit the growth of the various human tumor cell types is monitored and quantified.

10 Example 11: Evaluating the Efficacy of Retroviral Gene Therapy Vectors
Encoding Anti-Angiogenic Polypeptides for Treatment of
Ovarian Cancer Using In Vivo Gene Therapy

This example illustrates the feasibility of using retroviral gene therapy vectors encoding anti-angiogenic polypeptides to achieve efficient gene transfer to established tumors *in vivo* using a well-established murine model of human ovarian cancer. Following injections, mice are closely monitored for tumor growth and survival.

Eight to ten week old nude mice (Jackson Labs, Bar Harbor) are injected intra-peritoneally with 1×10^7 PA-1 cells, an ovarian cancer cell-line (ATCC), and followed until palpable tumors are identified. Viral supernatant for *in vivo* injection is prepared as follows: Viral producer cells are grown to confluence in DMEM with 10% bovine calf serum, and the medium is then changed. After 24 hours of incubation, the viral conditioned supernatant is filtered through a 0.45 μ m low protein binding filter, protamine sulfate is added to a final concentration of 6 μ g/ml, the solution is aliquoted into 2 ml volumes, and frozen at -80°C . Recipient mice receive three intraperitoneal injections of viral supernatant (2 mls per injection) in addition to the polycation, over a period of

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36 hours. Control mice are injected with medium collected from confluent dishes of NIH3T3 cells. Following injection of the viral conditioned supernatant, the mice are analyzed for survival as well as tumor growth over time as compared to mock injected controls. Results indicate that treatment of the ovarian cancer occurs. At death, the tumors are removed, weighed, and the cells dissociated for DNA extraction for Southern blot analysis to detect recombinant provirus.

Those skilled in the art will be able to ascertain using no more than routine experimentation, many equivalents of the specific embodiments of the invention described herein. These and all other equivalents are intended to be encompassed by the following claims.

In other embodiments, the invention provides methods and compositions for treating diseases and processes that are mediated by angiogenesis including, but not limited to, hemangioma, solid tumors, leukemia, metastasis, telangiectasia, psoriasis, scleroderma, pyogenic granuloma, myocardial angiogenesis, plaque neovascularization, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, corneal diseases, rubeosis, neovascular glaucoma, diabetic retinopathy, retrolental fibroplasia, arthritis, diabetic neovascularization, macular degeneration, wound healing, peptic ulcer, *Helicobacter* related diseases, fractures, keloids, vasculogenesis, hematopoiesis, ovulation, menstruation, placentation, and cat scratch fever.

What is claimed is:

CLAIMS

1. Use of a nucleic acid molecule which expresses an anti-angiogenic polypeptide selected from the group consisting of human angiostatin, murine angiostatin, human endostatin, murine endostatin, and angiogenesis-inhibiting fragments thereof in the preparation of a medicament for inhibiting tumor growth in a human patient harboring a solid tumor, wherein expression of the anti-angiogenic polypeptide in the patient inhibits angiogenesis in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells, thereby inhibiting its growth.

2. Use of a nucleic acid molecule which expresses an anti-angiogenic polypeptide of the formula A-B, wherein

A and B are polypeptide and/or export signal joined by a polypeptide and/or export signal bond;

A contains at least amino acids and comprises kringles 1, 2, and 3 of human or murine angiostatin; and

B contains at least amino acids and includes at least 75% of the amino acid sequence of human or murine endostatin in the preparation of a medicament for inhibiting tumor growth in a human patient harboring a solid tumor, wherein expression of the anti-angiogenic polypeptide in the patient inhibits angiogenesis in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells, thereby inhibiting its growth.

3. The use of claim 2, wherein A further comprises kringle region 4 of

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human or murine angiostatin.

4. The use of claim 2 or claim 3, wherein A further comprises kringle 5 of human or murine plasminogen.

5. The use of claim 1 or claim 2, wherein said nucleic acid molecule constitutes a portion of a viral vector.

6. The use of claim 1 or claim 2, wherein said nucleic acid molecule constitutes a portion of a plasmid.

7. The use of claim 6, wherein said plasmid is carried in a cell-free carrier so that the plasmid transfects living cells of the patient following plasmid administration, causing expression of the anti-angiogenesis polypeptide and/or export signal in the patient such that angiogenesis in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells is inhibited, causing inhibition of tumor growth.

8. The use of claim 6, wherein said plasmid has been transfected into animal cells *ex vivo*, wherein said animal cells express the anti-angiogenesis polypeptide to inhibit tumor-associated angiogenesis and tumor growth.

9. The use of claim 5, wherein said viral vector is carried in a cell-free carrier, so that the viral vector is incorporated into living cells of the patient following viral vector administration, causing expression of the anti-

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angiogenesis polypeptide in the patient such that angiogenesis in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells is inhibited, causing inhibition of tumor growth.

- 5 10. The use of claim 5, wherein animal cells are infected with said viral vector *ex vivo*, and then administered to said patient, wherein said animal cells express the anti-angiogenesis polypeptide to inhibit tumor-associated angiogenesis and tumor growth.
11. The use of claim 8, wherein said animal cells are human cells.
- 10 12. The use of claim 11, wherein said human cells are autologous.
13. The use of claim 11, wherein said human cells are allogeneic.
14. The use of claim 10, wherein said animal cells are human cells.
15. The use of claim 14, wherein said human cells are autologous.
16. The use of claim 14, wherein said human cells are allogeneic.
- 15 17. The use of claim 5, wherein said viral vector is a retroviral vector.
18. The use of claim 5, wherein said viral vector is a non-retroviral vector selected from the group consisting of adenoviral, adeno-associated, herpes, Simliki, Forest virus, and poxvirus vectors.

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19. The use of claim 17, wherein said retroviral vector is Murine Stem Cell Virus or a lentivirus.

20. The use of claim 1, wherein said angiostatin comprises kringles 1, 2 and 3.

5 21. The use of claim 20, wherein said angiostatin further comprises kringle 4.

22. The use of claim 1, wherein said anti-angiogenic polypeptide is a fusion of angiostatin or a biologically active fragment thereof and endostatin or a biologically active fragment thereof.

10 23. The use of claim 1, wherein said nucleic acid molecule includes a nucleotide sequence encoding a signal polypeptide and/or export signal for effecting secretion of said anti-angiogenesis polypeptide.

24. The use of claim 23, wherein said signal polypeptide and/or export signal is plasminogen signal polypeptide and/or export signal.

15 25. The use of claim 1, wherein said nucleic acid molecule includes a nucleotide sequence encoding a preactivation polypeptide and/or export signal for effecting Golgi and/or ER export of the anti-angiogenic polypeptide..

20 26. The use of claim 25, wherein said preactivation polypeptide and/or export signal is a preactivation polypeptide and/or export signal of a human protein of the blood coagulation cascade.

27. The use of claim 26, wherein said preactivation polypeptide and/or export signal is human plasminogen preactivation polypeptide and/or export signal.

28. The method of claim 25, wherein the preactivation encoding sequence is positioned between a signal-encoding sequence and the sequence encoding the anti-angiogenic polypeptide and/or export signal.

29. The use of claim 1, wherein said nucleic acid molecule includes a nucleotide sequence encoding a tag for identification of said anti-angiogenic polypeptide.

30. The method of claim 27, wherein said tag is a Flag tag polypeptide and/or export signal.

31. A viral gene therapy vector comprising a nucleic acid molecule which encodes an anti-angiogenic polypeptide selected from the group consisting of human angiostatin, murine angiostatin, human endostatin, murine endostatin, and angiogenesis-inhibiting fusions and fragments thereof, wherein said viral vector is sufficiently attenuated for use in human gene therapy.

32. A human cell infected with the vector of claim 31.

33. Use of a nucleic acid molecule which expresses in said patient an anti-angiogenic polypeptide selected from the group consisting of human angiostatin, murine angiostatin, human endostatin, murine endostatin, and angiogenesis-inhibiting fusions and fragments thereof, in the preparation of a

medicament for treating a human patient suffering from diabetic retinopathy, wherein expression of the anti-angiogenic polypeptide in the patient inhibits angiogenesis in the vicinity of the retina.

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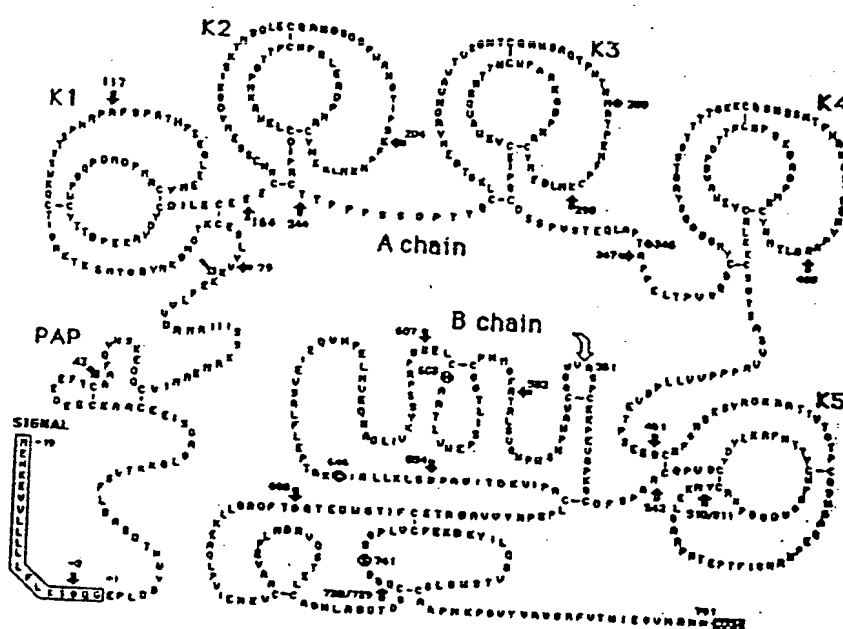


FIG. 1

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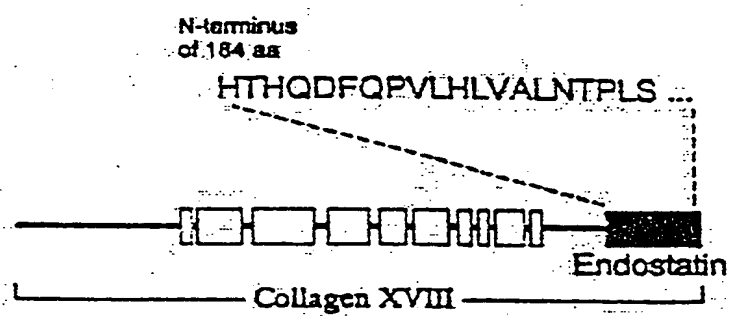


Fig. 2

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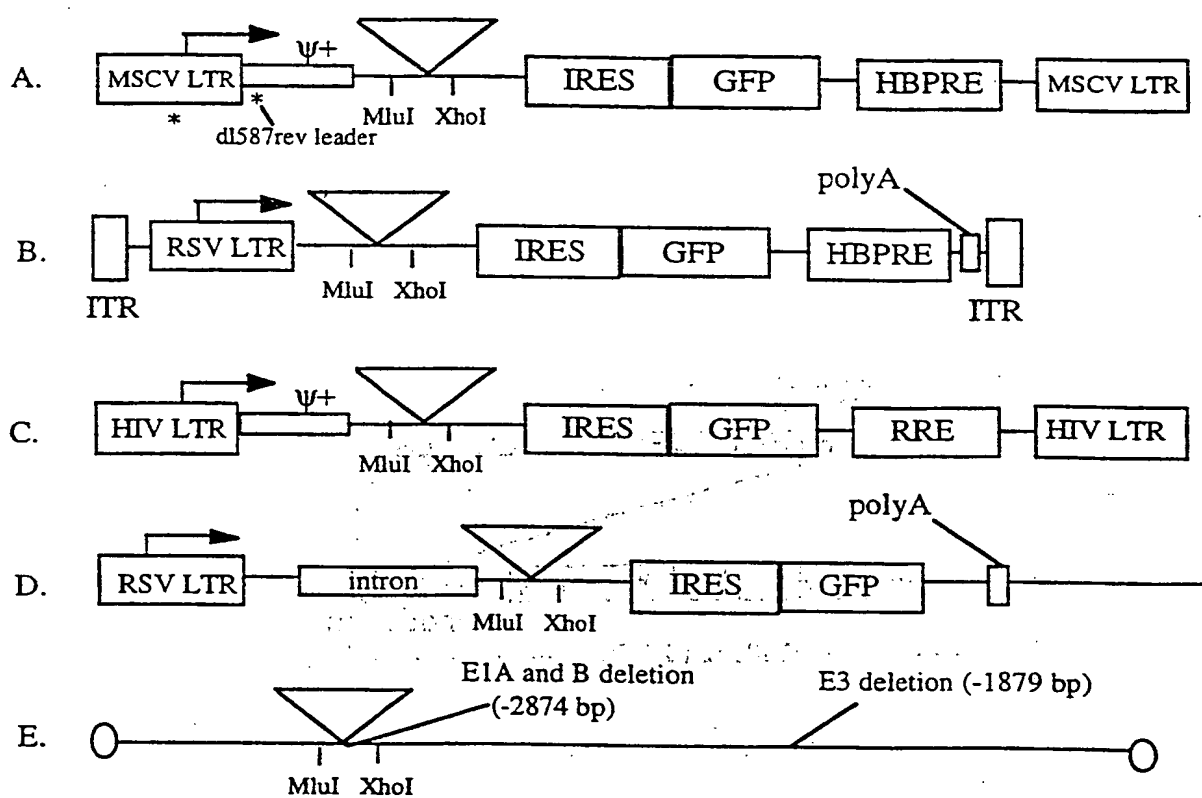


FIG. 3



FIG. 4

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→ **signal peptide** ← **preactivation peptide (PAP)** ← **human plasminogen**

ATGGAACATAAGGAAGTGGTCTCTCTACTCTCTTTATTTCTGAAATCAGCTCAAGGACAGCCCTCGGATGACTATGTGAATACCCAGGGGCTTCAGTGT
MetGluHisLysGluValValLeuLeuLeuLeuPheLeuLysSerGlyGlnGlyGluProLeuAspAspTyrValAlaSerThrGlnGlyAlaSerLeuPhe

TCAGTGTCTACTAAGAAGCAGCTGGGAGCAGGAAGTATAGAAGATGTGTCAGCAAAATGTGAGGAGGACGAAGAATTCACCTGCAGGGCATTCCAATATCA
SerValThrLysLysGlnLeuGlyAlaGlySerIleGluGluCysAlaAlaLysCysGluGluAspGluGluPheThrCysArgAlaPheGlnTyrHis

CAGTAAAGAGCAACAATGTGTGATAATGGCTGAAAACAGGAAGTCTCCATAATCATTAGGATGAGAGATGTAGTTTATTGTGAAAAGCAAGTGTATCTC
SerLysGluGlnGlnCysValIleMetAlaGluAsnArgLysSerSerIleIleArgMetArgAspValValLeuPheGluLysLysValTyrLeu

TCAGAGTGCAGACTGGGAAATGGAAGAAGTACAGAGGGAGCATGTCCAAAAAAGGATGCGATCAGCTTCAAAAATGGAAGTTCCTCTCCCCACA
SerGluCysLysThrGlyAsnGlyLysAsnTyrArgGlyThrMetSerLysThrLysAsnGlyIleThrCysGlnLysTrpSerSerThrSerProHisArg

GACCTAGATTCTCAGCTGCTACACACCCCTCAGAGGGAGTGGAGGAGAACTACTGCAGGAATCCAGACAACCATCGCAGGGGGCCCTGGTGTCTATCTAC
ProArgPheSerProAlaThrHisProSerGluGlyLeuGluGluAsnTyrCysArgAsnProAspAspAspProGlnGlyProTyrCysTyrThrThr

TGATCCAGAAAAGAGATATGACTACTGGACATCTCTGAGTGTGAAGAGGAATGTATGCGATTGAGTGGAGAAAATGACGGGCAAAATTTCCAGAGCC
AspProGluLysArgTyrAspTyrCysAspIleLeuGluCysGluGluGluCysMetHisCysSerGlyGluAsnTyrAspGlyLysIleSerLysThr

ATGCTCGGACTGGAAATGCCAGGCGCTGGGACTCTCAGAGCCACAGCTCATGGATACATTCCTTCCAAATTTCCAAAGAACCTGAAGAGAAATTAAT
MetSerGlyLeuGluCysGlnAlaTrpAspSerGlnSerProHisAlaHisGlyTyrIleProSerLysPheProAsnLysAsnLeuLysLysAsnTyrCys

GTCGTAAACCCGATAGGAGCTGCGGCTCTGGTGTTCACCCAGCCGCAACAAAGCGCTGGGAACTTTGGACATCCCCCGCTGCACACACCTCCACC
ArgAsnProAspArgGluLeuArgProTyrCysPheThrThrAspProAsnLysArgTrpGluLeuCysAspIleProArgCysThrThrProProPro

ATCTCTGCTCCACCTACAGTGTCTGAAGGAAACAGCTGAAATCTATCGCGGAAATGGCTGTACCTTTCCGGGACACCTGTCAGCACTGGAGT
SerSerGlyProThrTyrGlnCysLeuLysGlyThrGlyGluAsnTyrArgGlyAsnValAlaValThrValSerGlyHisThrCysGlnHisTrpSer

GCACAGACCCCTCACACATAACAGGACACCAAGAAATCTCCCTGCAAAAATTTGGATGAAAATCTACTGCGCAATCTGACGAAAAGGGCCCAT
AlaGlnThrProHisThrHisAsnArgThrProGluAsnPheProCysLysAsnLeuAspGluAsnTyrCysArgAsnProAspGlyLysArgAlaProTrp

GGTGCCATACAAACAGCCCAAGTGGCTGGGAGTACTGTAAATACCTGCTGTGACTCTCCCGAGTATCCAGGAACAATTTGGCTCCGACAGCACC
CysHisThrThrAsnSerGlnValArgTrpGluTyrCysLysIleProSerCysAspSerSerProValSerThrGluGlnLeuAlaProThrAlaPro

ACCTGAGCTAACCCCTGTGGTCCAGAGTGTACCATGTGATGGACAGAGCTACCGAGGCACATCTCCACCACCACACAGGAAGAAGTGTCACTGT
ProGluLeuThrProValValGlnAspCysTyrHisGlyAspGlyGlnSerTyrArgGlyThrSerSerThrThrThrGlyLysLysCysGlnSer

TGCTCATCTATGACACCCAGCCGACAGGAAGACCCAGAAAATACCCAAATGCTGGCGTGCAATGAACTACTGAGGAAATCCAGATGCCGATAAAG
TrpSerSerMetThrProHisArgHisGlnLysThrProGluAsnTyrProAsnAlaGlyLeuThrMetAsnTyrCysArgAsnProAspAlaAspLysGly

GCCCTCTGGTGTTTTACCACAGACCCAGCGTCAAGTGGAGTACTGCAACCTGAAAAATGCTCAGGAACAGAGCGAGTGTGTAGCACCTCCCGCTGT
ProTyrCysPheThrThrAspProSerValArgTrpGluTyrCysAsnLeuLysLysCysSerGlyThrGluAlaSerValValAlaProProVal

TGCTCTGCTTCCAGATGTAGAGACTCTCTCCGAAGAAGACTGTATGTTGGGAATGGGAAAGGATACCGAGGCAAGAGGGCGACCACTGTACTGGGAGC
ValLeuLeuProAspValGluThrProSerGluGluAspCysMetPheGlyAsnGlyLysGlyTyrArgGlyLysArgAlaThrThrValThrGlyThr

CCATGCCAGACTGGGCTGCCAGGAGCCCCATAGACACAGCATTTTCACTCCAGAGACAAATCCACGGCGGGTCTGGAAAAAATTAATGCGGTAAACC
ProCysGlnAspTrpAlaAlaGlnGluProHisArgHisSerIlePheThrProGluThrAsnProArgAlaGlyLeuGluLysAsnTyrCysArgAsnPro

CTGATGGTGATGTAGGTGCTCCCTGGTGCTACACGACAAATCCAGAAAATTTACGACTACTGTGATGCTCCCTAGTGTGGCGGCTTCATTTGATTG
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TGGGAAGCCTCAAGTGGAGCCGAAGAAATGCTCTGGAAGGTGTGGGGGGGTGTGTGGCCACCACATTCTTGGCCCTGGCAAGTCACTCTTAGAACA
GlyLysProGlnValGluProLysLysCysProGlyArgValValGlyGlyCysValAlaHisProHisSerTrpProTyrGlnValSerLeuArgThr

AGGTTTGGAATGCACCTTCTGTGGAGGCACCTTGATATCCAGAGTGGGTGTGACTGCTGCCACTGCTGGAGAGATCCCCAAGGCTTCATCTTACA
ArgPheGlyMetHisPheCysGlyGlyThrLeuIleSerProGluTrpValLeuThrAlaAlaHisCysLeuGluLysSerProArgProSerSerTyrLys

AGGTCATCTGGGTGCACCAAGAAGTGAATCTCGAACCGCATGTTCAGGAAATAGAAGTGTCTAGGCTGTCTTGGAGCCACACGAAAAGATATTGC
ValIleLeuGlyAlaHisGlnGluValAsnLeuGluProHisValGlnGluIleGluValSerArgLeuPheLeuGluProThrArgLysAspIleAla

CTTGCTAAAGCTAAGCAGCTCTGCCGTCACTACAGCAAGTAATCCAGCTGTCTGCTCCCAATATGTTGGTGTGCTGACCGGACCGAATGTTTC
LeuLeuLysLeuSerSerProAlaValIleThrAspLysValIleProAlaCysLeuProSerProAsnTyrValValAlaAspArgThrGluCysPhe

ATCACTGGCTGGGAGAGAACCCAGGTACTTTTGAGCTGGCCTTCAAGGAAAGCCAGCTCCCTGTGATTGAGATAAAGTGTGAATTCGCTATGAGT
IleThrGlyTrpGlyGluThrGlnGlyThrPheGlyAlaGlyLeuLeuLysGluAlaGlnLeuProValIleGluAsnLysValCysAsnArgTyrGluPhe

TTCTGAATGGAAGAGTCCAACTCCAGCACTGTGCTGGGCATTTGGCCGAGGACGACAGTTGCCAGGTGACAGTGGAGGCTCTCTGTTTCTCTT
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CGAGAAAGGACAAATACATTTTACAAGGAGTCACTCTTGGGGTCTTGTCTGTCAGCGCCCAATAGCCCTGGTGTCTATGTTCTGTTTCAAGGTTTGT
GluLysAspLysTyrIleLeuGlnGlyValThrSerTrpGlyLeuGlyCysAlaArgProAsnLysProGlyValTyrValArgValSerArgPheVal

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→ end human plasminogen coding sequence.

Fig. 5

7/8

Mouse Plasmidogen cDNA

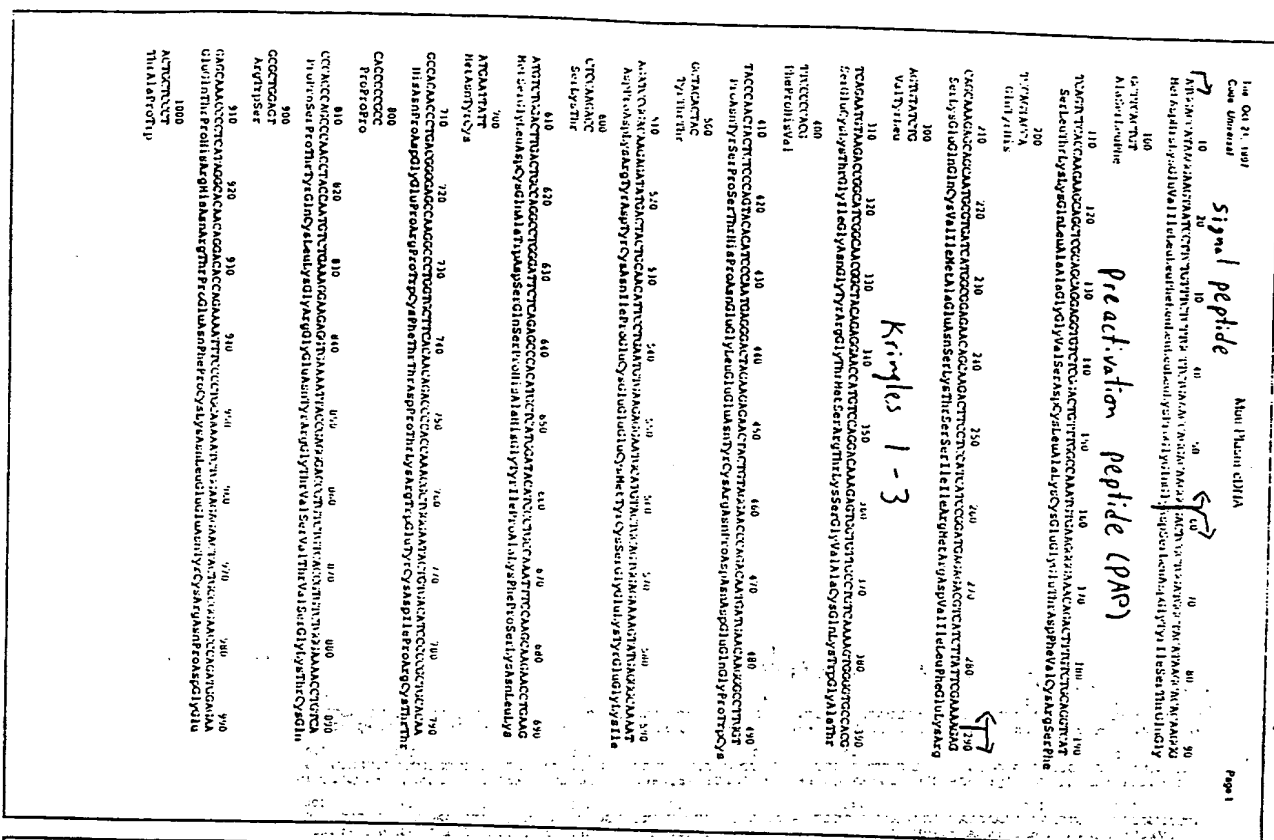
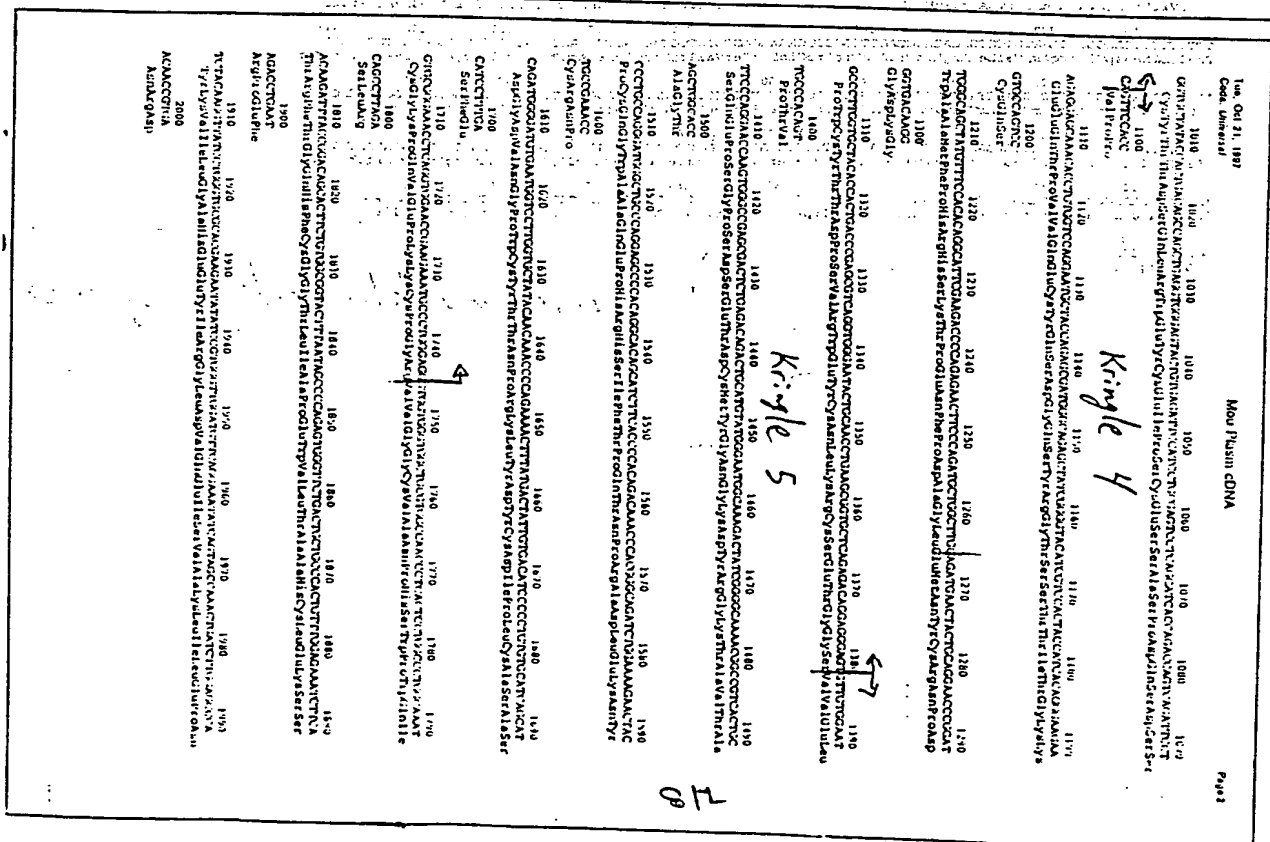


FIG. 7 (Sheet 1 of 2)



Tue, Oct 21, 1997
Code: Universal

Mou Plasm cDNA

Page 3

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CCGGACAAATA
ArgThrIle

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CysTyrIleThrGlyTrpGlyGluThrGlnGlyThrPheGlyAlaGlyArgLeuLysGluAlaGlnLeuProValIleGluAsnLysVal

2200
TGCAACCCGG
CysAsnArgVal

2210      2220      2230      2240      2250      2260      2270      2280      2290
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2300
GACCTCTGGT
ProLeuVal

2310      2320      2330      2340      2350      2360      2370      2380      2390
TTGCTTCGAGAAGGACAGTACATTTTACAAGGAGTCACTTCTTGGGGTCTTGGCTGTGCTCGCCCCAATAAGCCTGGTGTCTACGTTCTG
CysPheGluLysAspLysTyrIleLeuGlnGlyValThrSerTrpGlyLeuGlyCysAlaArgProAsnLysProGlyValTyrValArg

2400
TGTCTCAGCG
ValSerArg

2410      2420      2430      2440      2450      2460      2470      2480      2490
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PheValAspTrpIleGluArgGluMetArgAsnAspEndLeuGlyGlyArgProSerLysThrSerAlaTyrEndSerLeuLeuAsnMet

2500
GGGAGAGGGC
GlyArgGlyLeu

2510      2520      2530      2540      2550      2560      2570      2580      2590
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2600
TGTATTATTG
TyrTyrCys

2610      2620      2630      2640      2650      2660      2670      2680      2690
TGGGTAAAAATTTCTGTCTGTGGACTTCTGGATTCTGTGACAATAGACCATCACTGCTGTGACCTTTGTTGAAAAATAAACTCGATACTT
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2700
ACTTTG
Leu
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end plasminogen coding sequence.

FIG. 7 (Sheet 2 of 2)

SEQUENCE LISTING

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<120> ANTI-ANGIOGENIC GENE THERAPY VECTORS AND
THEIR USE IN TREATING ANGIOGENESIS-RELATED DISEASES

<130> 50033/002WO1

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Gly Gln Gly Glu Pro Leu Asp Asp Tyr Val Asn Thr Gln Gly Ala Ser

20

25

30

ctg ttc agt gtc act aag aag cag ctg gga gca gga agt ata gaa gaa
Leu Phe Ser Val Thr Lys Lys Gln Leu Gly Ala Gly Ser Ile Glu Glu

35

40

45

tgt gca gca aaa tgt gag gag gac gaa gaa ttc acc tgc agg gca ttc
Cys Ala Ala Lys Cys Glu Glu Asp Glu Glu Phe Thr Cys Arg Ala Phe

50

55

60

caa tat cac agt aaa gag caa caa tgt gtg ata atg gct gaa aac agg
Gln Tyr His Ser Lys Glu Gln Gln Cys Val Ile Met Ala Glu Asn Arg

65

70

75

80

aag tcc tcc ata atc att agg atg aga gat gta gtt tta ttt gaa aag
Lys Ser Ser Ile Ile Ile Arg Met Arg Asp Val Val Leu Phe Glu Lys

85

90

95

aaa gtg tat ctc tca gag tgc aag act ggg aat gga aag aac tac aga	336
Lys Val Tyr Leu Ser Glu Cys Lys Thr Gly Asn Gly Lys Asn Tyr Arg	
100 105 110	
ggg acg atg tcc aaa aca aaa aat ggc atc acc tgt caa aaa tgg agt	384
Gly Thr Met Ser Lys Thr Lys Asn Gly Ile Thr Cys Gln Lys Trp Ser	
115 120 125	
tcc act tct ccc cac aga cct aga ttc tca cct gct aca cac ccc tca	432
Ser Thr Ser Pro His Arg Pro Arg Phe Ser Pro Ala Thr His Pro Ser	
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gag gga ctg gag gag aac tac tgc agg aat cca gac aac gat ccg cag	480
Glu Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Pro Gln	
145 150 155 160	
ggg ccc tgg tgc tat act act gat cca gaa aag aga tat gac tac tgc	528
Gly Pro Trp Cys Tyr Thr Thr Asp Pro Glu Lys Arg Tyr Asp Tyr Cys	
165 170 175	
gac att ctt gag tgt gaa gag gaa tgt atg cat tgc agt gga gaa aac	576
Asp Ile Leu Glu Cys Glu Glu Glu Cys Met His Cys Ser Gly Glu Asn	
180 185 190	
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Tyr Asp Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Glu Cys Gln Ala	
195 200 205	
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Trp Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ser Lys Phe	
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225 230 235 240	
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Leu Arg Pro Trp Cys Phe Thr Thr Asp Pro Asn Lys Arg Trp Glu Leu	
245 250 255	
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Cys Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Ser Ser Gly Pro Thr	
260 265 270	
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Tyr Gln Cys Leu Lys Gly Thr Gly Glu Asn Tyr Arg Gly Asn Val Ala	
275 280 285	
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Val Thr Val Ser Gly His Thr Cys Gln His Trp Ser Ala Gln Thr Pro	
290 295 300	
cac aca cat aac agg aca cca gaa aac ttc ccc tgc aaa aat ttg gat	960
His Thr His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Asp	
305 310 315 320	

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 Glu Asn Tyr Cys Arg Asn Pro Asp Gly Lys Arg Ala Pro Trp Cys His
 325 330 335

aca acc aac agc caa gtg cgg tgg gag tac tgt aag ata ccg tcc tgt 1056
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 340 345 350

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 355 360 365

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 420 425 430

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 Lys Gly Pro Trp Cys Phe Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr
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 450 455 460

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gcg gcc cct tca ttt gat tgt ggg aag cct caa gtg gag ccg aag aaa			1728
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Cys Pro Gly Arg Val Val Gly Gly Cys Val Ala His Pro His Ser Trp			
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ctc cct gtg att gag aat aaa gtg tgc aat cgc tat gag ttt ctg aat			2208
Leu Pro Val Ile Glu Asn Lys Val Cys Asn Arg Tyr Glu Phe Leu Asn			
	725	730	735
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	740	745	750
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 Gln Tyr His Ser Lys Glu Gln Gln Cys Val Ile Met Ala Glu Asn Arg
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 Lys Ser Ser Ile Ile Ile Arg Met Arg Asp Val Val Leu Phe Glu Lys
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 Leu Phe Ser Leu Thr Lys Lys Gln Leu Ala Ala Gly Gly Val Ser Asp
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 Cys Leu Ala Lys Cys Glu Gly Glu Thr Asp Phe Val Cys Arg Ser Phe
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 Gln Tyr His Ser Lys Glu Gln Gln Cys Val Ile Met Ala Glu Asn Ser
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 Arg Val Tyr Leu Ser Glu Cys Lys Thr Gly Ile Gly Asn Gly Tyr Arg
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 Gly Thr Met Ser Arg Thr Lys Ser Gly Val Ala Cys Gln Lys Trp Gly

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Tyr Glu Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Asp Cys Gln Ala			
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Val Thr Val Ser Gly Lys Thr Cys Gln Arg Trp Ser Glu Gln Thr Pro			
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acc act gac agc cag ctg agg tgg gag tac tgt gag att cca tcc tgc			1056

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Cys Asn Leu Lys Arg Cys Ser Glu Thr Gly Gly Ser Val Val Glu Leu	
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Cys Met Tyr Gly Asn Gly Lys Asp Tyr Arg Gly Lys Thr Ala Val Thr	
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Ala Ala Gly Thr Pro Cys Gln Gly Trp Ala Ala Gln Glu Pro His Arg	
500 505 510	
cac agc atc ttc acc cca cag aca aac cca cgg gca gat ctg gaa aag	1584
His Ser Ile Phe Thr Pro Gln Thr Asn Pro Arg Ala Asp Leu Glu Lys	
515 520 525	
aac tac tgc cga aac cca gat ggg gat gtg aat ggt cct tgg tgc tat	1632
Asn Tyr Cys Arg Asn Pro Asp Gly Asp Val Asn Gly Pro Trp Cys Tyr	
530 535 540	
aca aca aac ccc aga aaa ctt tat gac tat tgt gac atc ccc ctg tgt	1680
Thr Thr Asn Pro Arg Lys Leu Tyr Asp Tyr Cys Asp Ile Pro Leu Cys	
545 550 555 560	

gca tca gca tca tcc ttt gag tgc ggg aaa cct cag gtg gaa ccg aag	1728
Ala Ser Ala Ser Ser Phe Glu Cys Gly Lys Pro Gln Val Glu Pro Lys	
565 570 575	
aaa tgc cct ggg agg gtg gtg ggt ggc tgc gtg gcc aac cct cac tcc	1776
Lys Cys Pro Gly Arg Val Val Gly Gly Cys Val Ala Asn Pro His Ser	
580 585 590	
tgg ccc tgg caa atc agc ctt aga aca aga ttt acc gga cag cac ttc	1824
Trp Pro Trp Gln Ile Ser Leu Arg Thr Arg Phe Thr Gly Gln His Phe	
595 600 605	
tgt ggc ggt act tta ata gcc cca gag tgg gtt ctg act gct gcc cac	1872
Cys Gly Gly Thr Leu Ile Ala Pro Glu Trp Val Leu Thr Ala Ala His	
610 615 620	
tgt ttg gag aaa tct tca aga cct gaa ttc tac aag gtt atc ctg ggt	1920
Cys Leu Glu Lys Ser Ser Arg Pro Glu Phe Tyr Lys Val Ile Leu Gly	
625 630 635 640	
gcg cac gaa gaa tat atc cgt ggg ttg gat gtt cag gaa ata tca gta	1968
Ala His Glu Glu Tyr Ile Arg Gly Leu Asp Val Gln Glu Ile Ser Val	
645 650 655	
gcc aaa ctg atc ttg gag ccc aac aac cgt gac att gcc ctg ctg aaa	2016
Ala Lys Leu Ile Leu Glu Pro Asn Asn Arg Asp Ile Ala Leu Leu Lys	
660 665 670	
cta agc cgc cca gcc acc atc acg gat aaa gtc att cca gct tgt ctg	2064
Leu Ser Arg Pro Ala Thr Ile Thr Asp Lys Val Ile Pro Ala Cys Leu	
675 680 685	
cca tct cca aat tac atg gtt gct gac cgg aca ata tgt tac atc acc	2112
Pro Ser Pro Asn Tyr Met Val Ala Asp Arg Thr Ile Cys Tyr Ile Thr	
690 695 700	
ggc tgg gga gag act caa ggg act ttc ggt gcc ggt cgt ctc aag gag	2160
Gly Trp Gly Glu Thr Gln Gly Thr Phe Gly Ala Gly Arg Leu Lys Glu	
705 710 715 720	
gct cag ctg cct gtg att gag aac aag gtg tgc aac cgc gtc gag tat	2208
Ala Gln Leu Pro Val Ile Glu Asn Lys Val Cys Asn Arg Val Glu Tyr	
725 730 735	
ctg aac aac aga gtc aaa tcc acg gag ctc tgt gcc ggg caa ctg gct	2256
Leu Asn Asn Arg Val Lys Ser Thr Glu Leu Cys Ala Gly Gln Leu Ala	
740 745 750	
ggc ggc gtc gac agc tgc caa ggc gac agt gga gga cct ctg gtt tgc	2304
Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys	
755 760 765	
ttc gag aag gac aag tac att tta caa gga gtc act tct tgg ggt ctt	2352
Phe Glu Lys Asp Lys Tyr Ile Leu Gln Gly Val Thr Ser Trp Gly Leu	
770 775 780	

ggc tgt gct cgc ccc aat aag cct ggt gtc tac gtt cgt gtc tca cgg 2400
 Gly Cys Ala Arg Pro Asn Lys Pro Gly Val Tyr Val Arg Val Ser Arg
 785 790 795 800

ttt gtt gat tgg att gaa agg gag atg agg aat aac tgactaggtg 2446
 Phe Val Asp Trp Ile Glu Arg Glu Met Arg Asn Asn
 805 810

gaaggccgag caaacctct gcttactaaa gcttactgaa tatggggaga gggcttaggg 2506
 tgtttgga aaactgacagt aatcaaactg ggacactaca ctgaaccaca gcttctgtgc 2566
 gccctcagc cctccctt tttttgtatt attgtgggta aaattttcct gtctgtggac 2626
 ttctggattt tgtgacaata gaccatcact gctgtgacct ttgttgaaaa taaactcgat 2686
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<210> 4

<211> 812

<212> PRT

<213> Mus musculus

<400> 4

Met Asp His Lys Glu Val Ile Leu Leu Phe Leu Leu Leu Lys Pro
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 20 25 30
 Leu Phe Ser Leu Thr Lys Lys Gln Leu Ala Ala Gly Gly Val Ser Asp
 35 40 45
 Cys Leu Ala Lys Cys Glu Gly Glu Thr Asp Phe Val Cys Arg Ser Phe
 50 55 60
 Gln Tyr His Ser Lys Glu Gln Gln Cys Val Ile Met Ala Glu Asn Ser
 65 70 75 80
 Lys Thr Ser Ser Ile Ile Arg Met Arg Asp Val Ile Leu Phe Glu Lys
 85 90 95
 Arg Val Tyr Leu Ser Glu Cys Lys Thr Gly Ile Gly Asn Gly Tyr Arg
 100 105 110
 Gly Thr Met Ser Arg Thr Lys Ser Gly Val Ala Cys Gln Lys Trp Gly
 115 120 125
 Ala Thr Phe Pro His Val Pro Asn Tyr Ser Pro Ser Thr His Pro Asn
 130 135 140
 Glu Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Glu Gln
 145 150 155 160
 Gly Pro Trp Cys Tyr Thr Thr Asp Pro Asp Lys Arg Tyr Asp Tyr Cys
 165 170 175
 Asn Ile Pro Glu Cys Glu Glu Glu Cys Met Tyr Cys Ser Gly Glu Lys
 180 185 190
 Tyr Glu Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Asp Cys Gln Ala
 195 200 205
 Trp Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ala Lys Phe
 210 215 220
 Pro Ser Lys Asn Leu Lys Met Asn Tyr Cys His Asn Pro Asp Gly Glu
 225 230 235 240
 Pro Arg Pro Trp Cys Phe Thr Thr Asp Pro Thr Lys Arg Trp Glu Tyr
 245 250 255
 Cys Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Pro Ser Pro Thr
 260 265 270

Tyr Gln Cys Leu Lys Gly Arg Gly Glu Asn Tyr Arg Gly Thr Val Ser
 275 280 285
 Val Thr Val Ser Gly Lys Thr Cys Gln Arg Trp Ser Glu Gln Thr Pro
 290 295 300
 His Arg His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Glu
 305 310 315 320
 Glu Asn Tyr Cys Arg Asn Pro Asp Gly Glu Thr Ala Pro Trp Cys Tyr
 325 330 335
 Thr Thr Asp Ser Gln Leu Arg Trp Glu Tyr Cys Glu Ile Pro Ser Cys
 340 345 350
 Glu Ser Ser Ala Ser Pro Asp Gln Ser Asp Ser Ser Val Pro Pro Glu
 355 360 365
 Glu Gln Thr Pro Val Val Gln Glu Cys Tyr Gln Ser Asp Gly Gln Ser
 370 375 380
 Tyr Arg Gly Thr Ser Ser Thr Thr Ile Thr Gly Lys Lys Cys Gln Ser
 385 390 395 400
 Trp Ala Ala Met Phe Pro His Arg His Ser Lys Thr Pro Glu Asn Phe
 405 410 415
 Pro Asp Ala Gly Leu Glu Met Asn Tyr Cys Arg Asn Pro Asp Gly Asp
 420 425 430
 Lys Gly Pro Trp Cys Tyr Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr
 435 440 445
 Cys Asn Leu Lys Arg Cys Ser Glu Thr Gly Gly Ser Val Val Glu Leu
 450 455 460
 Pro Thr Val Ser Gln Glu Pro Ser Gly Pro Ser Asp Ser Glu Thr Asp
 465 470 475 480
 Cys Met Tyr Gly Asn Gly Lys Asp Tyr Arg Gly Lys Thr Ala Val Thr
 485 490 495
 Ala Ala Gly Thr Pro Cys Gln Gly Trp Ala Ala Gln Glu Pro His Arg
 500 505 510
 His Ser Ile Phe Thr Pro Gln Thr Asn Pro Arg Ala Asp Leu Glu Lys
 515 520 525
 Asn Tyr Cys Arg Asn Pro Asp Gly Asp Val Asn Gly Pro Trp Cys Tyr
 530 535 540
 Thr Thr Asn Pro Arg Lys Leu Tyr Asp Tyr Cys Asp Ile Pro Leu Cys
 545 550 555 560
 Ala Ser Ala Ser Ser Phe Glu Cys Gly Lys Pro Gln Val Glu Pro Lys
 565 570 575
 Lys Cys Pro Gly Arg Val Val Gly Gly Cys Val Ala Asn Pro His Ser
 580 585 590
 Trp Pro Trp Gln Ile Ser Leu Arg Thr Arg Phe Thr Gly Gln His Phe
 595 600 605
 Cys Gly Gly Thr Leu Ile Ala Pro Glu Trp Val Leu Thr Ala Ala His
 610 615 620
 Cys Leu Glu Lys Ser Ser Arg Pro Glu Phe Tyr Lys Val Ile Leu Gly
 625 630 635 640
 Ala His Glu Glu Tyr Ile Arg Gly Leu Asp Val Gln Glu Ile Ser Val
 645 650 655
 Ala Lys Leu Ile Leu Glu Pro Asn Asn Arg Asp Ile Ala Leu Leu Lys
 660 665 670
 Leu Ser Arg Pro Ala Thr Ile Thr Asp Lys Val Ile Pro Ala Cys Leu
 675 680 685
 Pro Ser Pro Asn Tyr Met Val Ala Asp Arg Thr Ile Cys Tyr Ile Thr
 690 695 700
 Gly Trp Gly Glu Thr Gln Gly Thr Phe Gly Ala Gly Arg Leu Lys Glu

705 710 715 720
 Ala Gln Leu Pro Val Ile Glu Asn Lys Val Cys Asn Arg Val Glu Tyr
 725 730 735
 Leu Asn Asn Arg Val Lys Ser Thr Glu Leu Cys Ala Gly Gln Leu Ala
 740 745 750
 Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys
 755 760 765
 Phe Glu Lys Asp Lys Tyr Ile Leu Gln Gly Val Thr Ser Trp Gly Leu
 770 775 780
 Gly Cys Ala Arg Pro Asn Lys Pro Gly Val Tyr Val Arg Val Ser Arg
 785 790 795 800
 Phe Val Asp Trp Ile Glu Arg Glu Met Arg Asn Asn
 805 810

<210> 5
 <211> 1083
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)...(1083)

<400> 5
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 Tyr Leu Ser Glu Cys Lys Thr Gly Asn Gly Lys Asn Tyr Arg Gly Thr
 1 5 10 15
 atg tcc aaa aca aaa aat ggc atc acc tgt caa aaa tgg agt tcc act 96
 Met Ser Lys Thr Lys Asn Gly Ile Thr Cys Gln Lys Trp Ser Ser Thr
 20 25 30
 tct ccc cac aga cct aga ttc tca cct gct aca cac ccc tca gag gga 144
 Ser Pro His Arg Pro Arg Phe Ser Pro Ala Thr His Pro Ser Glu Gly
 35 40 45
 ctg gag gag aac tac tgc agg aat cca gac aac gat ccg cag ggg ccc 192
 Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Pro Gln Gly Pro
 50 55 60
 tgg tgc tat act act gat cca gaa aag aga tat gac tac tgc gac att 240
 Trp Cys Tyr Thr Thr Asp Pro Glu Lys Arg Tyr Asp Tyr Cys Asp Ile
 65 70 75 80
 ctt gag tgt gaa gag gaa tgt atg cat tgc agt gga gaa aac tat gac 288
 Leu Glu Cys Glu Glu Glu Cys Met His Cys Ser Gly Glu Asn Tyr Asp
 85 90 95
 ggc aaa att tcc aag acc atg tct gga ctg gaa tgc cag gcc tgg gac 336
 Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Glu Cys Gln Ala Trp Asp
 100 105 110
 tct cag agc cca cac gct cat gga tac att cct tcc aaa ttt cca aac 384
 Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ser Lys Phe Pro Asn
 115 120 125

aag aac ctg aag aag aat tac tgt cgt aac ccc gat agg gag ctg cgg	432
Lys Asn Leu Lys Lys Asn Tyr Cys Arg Asn Pro Asp Arg Glu Leu Arg	
130 135 140	
cct tgg tgt ttc acc acc gac ccc aac aag cgc tgg gaa ctt tgc gac	480
Pro Trp Cys Phe Thr Thr Asp Pro Asn Lys Arg Trp Glu Leu Cys Asp	
145 150 155 160	
atc ccc cgc tgc aca aca cct cca cca tct tct ggt ccc acc tac cag	528
Ile Pro Arg Cys Thr Thr Pro Pro Pro Ser Ser Gly Pro Thr Tyr Gln	
165 170 175	
tgt ctg aag gga aca ggt gaa aac tat cgc ggg aat gtg gct gtt acc	576
Cys Leu Lys Gly Thr Gly Glu Asn Tyr Arg Gly Asn Val Ala Val Thr	
180 185 190	
gtt tcc ggg cac acc tgt cag cac tgg agt gca cag acc cct cac aca	624
Val Ser Gly His Thr Cys Gln His Trp Ser Ala Gln Thr Pro His Thr	
195 200 205	
cat aac agg aca cca gaa aac ttc ccc tgc aaa aat ttg gat gaa aac	672
His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Asp Glu Asn	
210 215 220	
tac tgc cgc aat cct gac gga aaa agg gcc cca tgg tgc cat aca acc	720
Tyr Cys Arg Asn Pro Asp Gly Lys Arg Ala Pro Trp Cys His Thr Thr	
225 230 235 240	
aac agc caa gtg cgg tgg gag tac tgt aag ata ccg tcc tgt gac tcc	768
Asn Ser Gln Val Arg Trp Glu Tyr Cys Lys Ile Pro Ser Cys Asp Ser	
245 250 255	
tcc cca gta tcc acg gaa caa ttg gct ccc aca gca cca cct gag cta	816
Ser Pro Val Ser Thr Glu Gln Leu Ala Pro Thr Ala Pro Pro Glu Leu	
260 265 270	
acc cct gtg gtc cag gac tgc tac cat ggt gat gga cag agc tac cga	864
Thr Pro Val Val Gln Asp Cys Tyr His Gly Asp Gly Gln Ser Tyr Arg	
275 280 285	
ggc aca tcc tcc acc acc acc aca gga aag aag tgt cag tct tgg tca	912
Gly Thr Ser Ser Thr Thr Thr Gly Lys Lys Cys Gln Ser Trp Ser	
290 295 300	
tct atg aca cca cac cgg cac cag aag acc cca gaa aac tac cca aat	960
Ser Met Thr Pro His Arg His Gln Lys Thr Pro Glu Asn Tyr Pro Asn	
305 310 315 320	
gct ggc ctg aca atg aac tac tgc agg aat cca gat gcc gat aaa ggc	1008
Ala Gly Leu Thr Met Asn Tyr Cys Arg Asn Pro Asp Ala Asp Lys Gly	
325 330 335	
ccc tgg tgt ttt acc aca gac ccc agc gtc agg tgg gag tac tgc aac	1056
Pro Trp Cys Phe Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr Cys Asn	

340 345 350
 ctg aaa aaa tgc tca gga aca gaa gcg 1083
 Leu Lys Lys Cys Ser Gly Thr Glu Ala
 355 360
 <210> 6
 <211> 361
 <212> PRT
 <213> Homo sapiens
 <400> 6
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 Met Ser Lys Thr Lys Asn Gly Ile Thr Cys Gln Lys Trp Ser Ser Thr
 20 25 30
 Ser Pro His Arg Pro Arg Phe Ser Pro Ala Thr His Pro Ser Glu Gly
 35 40 45
 Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Pro Gln Gly Pro
 50 55 60
 Trp Cys Tyr Thr Thr Asp Pro Glu Lys Arg Tyr Asp Tyr Cys Asp Ile
 65 70 75 80
 Leu Glu Cys Glu Glu Glu Cys Met His Cys Ser Gly Glu Asn Tyr Asp
 85 90 95
 Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Glu Cys Gln Ala Trp Asp
 100 105 110
 Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ser Lys Phe Pro Asn
 115 120 125
 Lys Asn Leu Lys Lys Asn Tyr Cys Arg Asn Pro Asp Arg Glu Leu Arg
 130 135 140
 Pro Trp Cys Phe Thr Thr Asp Pro Asn Lys Arg Trp Glu Leu Cys Asp
 145 150 155 160
 Ile Pro Arg Cys Thr Thr Pro Pro Pro Ser Ser Gly Pro Thr Tyr Gln
 165 170 175
 Cys Leu Lys Gly Thr Gly Glu Asn Tyr Arg Gly Asn Val Ala Val Thr
 180 185 190
 Val Ser Gly His Thr Cys Gln His Trp Ser Ala Gln Thr Pro His Thr
 195 200 205
 His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Asp Glu Asn
 210 215 220
 Tyr Cys Arg Asn Pro Asp Gly Lys Arg Ala Pro Trp Cys His Thr Thr
 225 230 235 240
 Asn Ser Gln Val Arg Trp Glu Tyr Cys Lys Ile Pro Ser Cys Asp Ser
 245 250 255
 Ser Pro Val Ser Thr Glu Gln Leu Ala Pro Thr Ala Pro Pro Glu Leu
 260 265 270
 Thr Pro Val Val Gln Asp Cys Tyr His Gly Asp Gly Gln Ser Tyr Arg
 275 280 285
 Gly Thr Ser Ser Thr Thr Thr Thr Gly Lys Lys Cys Gln Ser Trp Ser
 290 295 300
 Ser Met Thr Pro His Arg His Gln Lys Thr Pro Glu Asn Tyr Pro Asn
 305 310 315 320
 Ala Gly Leu Thr Met Asn Tyr Cys Arg Asn Pro Asp Ala Asp Lys Gly
 325 330 335

Pro Trp Cys Phe Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr Cys Asn
 340 345 350
 Leu Lys Lys Cys Ser Gly Thr Glu Ala
 355 360

<210> 7
 <211> 1086
 <212> DNA
 <213> Mus musculus

<220>
 <221> CDS
 <222> (1)...(1086)

<400> 7
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 1 5 10 15
 acc atg tcc agg aca aag agt ggt gtt gcc tgt caa aag tgg ggt gcc 96
 Thr Met Ser Arg Thr Lys Ser Gly Val Ala Cys Gln Lys Trp Gly Ala
 20 25 30
 acg ttc ccc cac gta ccc aac tac tct ccc agt aca cat ccc aat gag 144
 Thr Phe Pro His Val Pro Asn Tyr Ser Pro Ser Thr His Pro Asn Glu
 35 40 45
 gga cta gaa gag aac tac tgt agg aac cca gac aat gat gaa caa ggg 192
 Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Glu Gln Gly
 50 55 60
 cct tgg tgc tac act aca gat ccg gac aag aga tat gac tac tgc aac 240
 Pro Trp Cys Tyr Thr Thr Asp Pro Asp Lys Arg Tyr Asp Tyr Cys Asn
 65 70 75 80
 att cct gaa tgt gaa gag gaa tgc atg tac tgc agt gga gaa aag tat 288
 Ile Pro Glu Cys Glu Glu Glu Cys Met Tyr Cys Ser Gly Glu Lys Tyr
 85 90 95
 gag ggc aaa atc tcc aag acc atg tct gga ctt gac tgc cag gcc tgg 336
 Glu Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Asp Cys Gln Ala Trp
 100 105 110
 gat tct cag agc cca cat gct cat gga tac atc cct gcc aaa ttt cca 384
 Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ala Lys Phe Pro
 115 120 125
 agc aag aac ctg aag atg aat tat tgc cac aac cct gac ggg gag cca 432
 Ser Lys Asn Leu Lys Met Asn Tyr Cys His Asn Pro Asp Gly Glu Pro
 130 135 140
 agg ccc tgg tgc ttc aca aca gac ccc acc aaa cgc tgg gaa tac tgt 480
 Arg Pro Trp Cys Phe Thr Thr Asp Pro Thr Lys Arg Trp Glu Tyr Cys
 145 150 155 160

gac atc ccc cgc tgc aca aca ccc ccg ccc cca ccc agc cca acc tac 528
 Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Pro Ser Pro Thr Tyr
 165 170 175

caa tgt ctg aaa gga aga ggt gaa aat tac cga ggg acc gtg tct gtc 576
 Gln Cys Leu Lys Gly Arg Gly Glu Asn Tyr Arg Gly Thr Val Ser Val
 180 185 190

acc gtg tct ggg aaa acc tgt cag cgc tgg agt gag caa acc cct cat 624
 Thr Val Ser Gly Lys Thr Cys Gln Arg Trp Ser Glu Gln Thr Pro His
 195 200 205

agg cac aac agg aca cca gaa aat ttc ccc tgc aaa aat ctg gaa gag 672
 Arg His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Glu Glu
 210 215 220

aac tac tgc cgg aac cca gat gga gaa act gct ccc tgg tgc tat acc 720
 Asn Tyr Cys Arg Asn Pro Asp Gly Glu Thr Ala Pro Trp Cys Tyr Thr
 225 230 235 240

act gac agc cag ctg agg tgg gag tac tgt gag att cca tcc tgc gag 768
 Thr Asp Ser Gln Leu Arg Trp Glu Tyr Cys Glu Ile Pro Ser Cys Glu
 245 250 255

tcc tca gca tca cca gac cag tca gat tcc tca gtt cca cca gag gag 816
 Ser Ser Ala Ser Pro Asp Gln Ser Asp Ser Ser Val Pro Pro Glu Glu
 260 265 270

caa aca cct gtg gtc cag gaa tgc tac cag agc gat ggg cag agc tat 864
 Gln Thr Pro Val Val Gln Glu Cys Tyr Gln Ser Asp Gly Gln Ser Tyr
 275 280 285

cgg ggt aca tgc tcc act acc atc aca ggg aag aag tgc cag tcc tgg 912
 Arg Gly Thr Ser Ser Thr Thr Ile Thr Gly Lys Lys Cys Gln Ser Trp
 290 295 300

gca gct atg ttt cca cac agg cat tgc aag acc cca gag aac ttc cca 960
 Ala Ala Met Phe Pro His Arg His Ser Lys Thr Pro Glu Asn Phe Pro
 305 310 315 320

gat gct ggc ttg gag atg aac tac tgc agg aac ccg gat ggt gac aag 1008
 Asp Ala Gly Leu Glu Met Asn Tyr Cys Arg Asn Pro Asp Gly Asp Lys
 325 330 335

ggc cct tgg tgc tac acc act gac ccg agc gtc agg tgg gaa tac tgc 1056
 Gly Pro Trp Cys Tyr Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr Cys
 340 345 350

aac ctc aag cgg tgc tca gag aca gga ggg 1086
 Asn Leu Lys Arg Cys Ser Glu Thr Gly Gly
 355 360

<10> 8

<11> 362

<212> PRT

<213> Mus musculus

<400> 8

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 20          25          30
Thr Phe Pro His Val Pro Asn Tyr Ser Pro Ser Thr His Pro Asn Glu
 35          40          45
Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Glu Gln Gly
 50          55          60
Pro Trp Cys Tyr Thr Thr Asp Pro Asp Lys Arg Tyr Asp Tyr Cys Asn
 65          70          75          80
Ile Pro Glu Cys Glu Glu Glu Cys Met Tyr Cys Ser Gly Glu Lys Tyr
 85          90          95
Glu Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Asp Cys Gln Ala Trp
100          105          110
Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ala Lys Phe Pro
115          120          125
Ser Lys Asn Leu Lys Met Asn Tyr Cys His Asn Pro Asp Gly Glu Pro
130          135          140
Arg Pro Trp Cys Phe Thr Thr Asp Pro Thr Lys Arg Trp Glu Tyr Cys
145          150          155          160
Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Pro Pro Ser Pro Thr Tyr
165          170          175
Gln Cys Leu Lys Gly Arg Gly Glu Asn Tyr Arg Gly Thr Val Ser Val
180          185          190
Thr Val Ser Gly Lys Thr Cys Gln Arg Trp Ser Glu Gln Thr Pro His
195          200          205
Arg His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Glu Glu
210          215          220
Asn Tyr Cys Arg Asn Pro Asp Gly Glu Thr Ala Pro Trp Cys Tyr Thr
225          230          235          240
Thr Asp Ser Gln Leu Arg Trp Glu Tyr Cys Glu Ile Pro Ser Cys Glu
245          250          255
Ser Ser Ala Ser Pro Asp Gln Ser Asp Ser Ser Val Pro Pro Glu Glu
260          265          270
Gln Thr Pro Val Val Gln Glu Cys Tyr Gln Ser Asp Gly Gln Ser Tyr
275          280          285
Arg Gly Thr Ser Ser Thr Thr Ile Thr Gly Lys Lys Cys Gln Ser Trp
290          295          300
Ala Ala Met Phe Pro His Arg His Ser Lys Thr Pro Glu Asn Phe Pro
305          310          315          320
Asp Ala Gly Leu Glu Met Asn Tyr Cys Arg Asn Pro Asp Gly Asp Lys
325          330          335
Gly Pro Trp Cys Tyr Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr Cys
340          345          350
Asn Leu Lys Arg Cys Ser Glu Thr Gly Gly
355          360

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<210> 9

<211> 552

<212> DNA

<213> Mus musculus

<220>

<221> CDS

<222> (1) ... (552)

<400> 9

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cat act cat cag gac ttt cag cca gtg ctc cac ctg gtg gca ctg aac      48
His Thr His Gln Asp Phe Gln Pro Val Leu His Leu Val Ala Leu Asn
1          5          10          15
acc ccc ctg tct gga ggc atg cgt ggt atc cgt gga gca gat ttc cag      96
Thr Pro Leu Ser Gly Gly Met Arg Gly Ile Arg Gly Ala Asp Phe Gln
          20          25          30
tgc ttc cag caa gcc cga gcc gtg ggg ctg tcg ggc acc ttc cgg gct      144
Cys Phe Gln Ala Arg Ala Val Gly Leu Ser Gly Thr Phe Arg Ala
          35          40          45
ttc ctg tcc tct agg ctg cag gat ctc tat agc atc gtg cgc cgt gct      192
Phe Leu Ser Ser Arg Leu Gln Asp Leu Tyr Ser Ile Val Arg Arg Ala
          50          55          60
gac cgg ggg tct gtg ccc atc gtc aac ctg aag gac gag gtg cta tct      240
Asp Arg Gly Ser Val Pro Ile Val Asn Leu Lys Asp Glu Val Leu Ser
65          70          75          80
ccc agc tgg gac tcc ctg ttt tct ggc tcc cag ggt caa gtg caa ccc      288
Pro Ser Trp Asp Ser Leu Phe Ser Gly Ser Gln Gly Gln Val Gln Pro
          85          90          95
ggg gcc cgc atc ttt tct ttt gac ggc aga gat gtc ctg aga cac cca      336
Gly Ala Arg Ile Phe Ser Phe Asp Gly Arg Asp Val Leu Arg His Pro
          100          105          110
gcc tgg ccg cag aag agc gta tgg cac ggc tcg gac ccc agt ggg cgg      384
Ala Trp Pro Gln Lys Ser Val Trp His Gly Ser Asp Pro Ser Gly Arg
          115          120          125
agg ctg atg gag agt tac tgt gag aca tgg cga act gaa act act ggg      432
Arg Leu Met Glu Ser Tyr Cys Glu Thr Trp Arg Thr Glu Thr Thr Gly
          130          135          140
gct aca ggt cag gcc tcc tcc ctg ctg tca ggc agg ctc ctg gaa cag      480
Ala Thr Gly Gln Ala Ser Ser Leu Leu Ser Gly Arg Leu Leu Glu Gln
          145          150          155          160
aaa gct gcg agc tgc cac aac agc tac atc gtc ctg tgc att gag aat      528
Lys Ala Ala Ser Cys His Asn Ser Tyr Ile Val Leu Cys Ile Glu Asn
          165          170          175
agc ttc atg acc tct ttc tcc aaa      552
Ser Phe Met Thr Ser Phe Ser Lys
          180

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<210> 10

<211> 184
 <212> PRT
 <213> Mus musculus

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 20 25 30
 Cys Phe Gln Gln Ala Arg Ala Val Gly Leu Ser Gly Thr Phe Arg Ala
 35 40 45
 Phe Leu Ser Ser Arg Leu Gln Asp Leu Tyr Ser Ile Val Arg Arg Ala
 50 55 60
 Asp Arg Gly Ser Val Pro Ile Val Asn Leu Lys Asp Glu Val Leu Ser
 65 70 75 80
 Pro Ser Trp Asp Ser Leu Phe Ser Gly Ser Gln Gly Gln Val Gln Pro
 85 90 95
 Gly Ala Arg Ile Phe Ser Phe Asp Gly Arg Asp Val Leu Arg His Pro
 100 105 110
 Ala Trp Pro Gln Lys Ser Val Trp His Gly Ser Asp Pro Ser Gly Arg
 115 120 125
 Arg Leu Met Glu Ser Tyr Cys Glu Thr Trp Arg Thr Glu Thr Thr Gly
 130 135 140
 Ala Thr Gly Gln Ala Ser Ser Leu Leu Ser Gly Arg Leu Leu Glu Gln
 145 150 155 160
 Lys Ala Ala Ser Cys His Asn Ser Tyr Ile Val Leu Cys Ile Glu Asn
 165 170 175
 Ser Phe Met Thr Ser Phe Ser Lys
 180

<210> 11
 <211> 1414
 <212> DNA
 <213> Mus musculus

<220>
 <221> CDS
 <222> (1)...(1414)

<400> 11
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 Met Asp His Lys Glu Val Ile Leu Leu Phe Leu Leu Leu Lys Pro
 1 5 10 15
 gga caa ggg gac tcg ctg gat ggc tac ata agc aca caa ggg gct tca 96
 Gly Gln Gly Asp Ser Leu Asp Gly Tyr Ile Ser Thr Gln Gly Ala Ser
 20 25 30
 ctg ttc agt ctc acc aag aag cag ctc gca gca gga ggt gtc tcg gac 144
 Leu Phe Ser Leu Thr Lys Lys Gln Leu Ala Ala Gly Gly Val Ser Asp
 35 40 45
 tgt tgg gcc aaa tgt gaa ggg gaa aca gac ttt gtc tgc agg tca ttc 192
 Cys Leu Ala Lys Cys Glu Gly Glu Thr Asp Phe Val Cys Arg Ser Phe
 50 55 60

cag tac cac agc aaa gag cag caa tgc gtg atc atg gcg gag aac agc	240
Gln Tyr His Ser Lys Glu Gln Gln Cys Val Ile Met Ala Glu Asn Ser	
65 70 75 80	
aag act tcc tcc atc atc cgg atg aga gac gtc atc tta ttc gaa aag	288
Lys Thr Ser Ser Ile Arg Met Arg Asp Val Ile Leu Phe Glu Lys	
85 90 95	
aga gtg tat ctg tca gaa tgt aag acc ggc atc ggc aac ggc tac aga	336
Arg Val Tyr Leu Ser Glu Cys Lys Thr Gly Ile Gly Asn Gly Tyr Arg	
100 105 110	
gga acc atg tcc agg aca aag agt ggt gtt gcc tgt caa aag tgg ggt	384
Gly Thr Met Ser Arg Thr Lys Ser Gly Val Ala Cys Gln Lys Trp Gly	
115 120 125	
gcc acg ttc ccc cac gta ccc aac tac tct ccc agt aca cat ccc aat	432
Ala Thr Phe Pro His Val Pro Asn Tyr Ser Pro Ser Thr His Pro Asn	
130 135 140	
gag gga cta gaa gag aac tac tgt agg aac cca gac aat gat gaa caa	480
Glu Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Glu Gln	
145 150 155 160	
ggg cct tgg tgc tac act aca gat ccg gac aag aga tat gac tac tgc	528
Gly Pro Trp Cys Tyr Thr Thr Asp Pro Asp Lys Arg Tyr Asp Tyr Cys	
165 170 175	
aac att cct gaa tgt gaa gag gaa tgc atg tac tgc agt gga gaa aag	576
Asn Ile Pro Glu Cys Glu Glu Glu Cys Met Tyr Cys Ser Gly Glu Lys	
180 185 190	
tat gag ggc aaa atc tcc aag acc atg tct gga ctt gac tgc cag gcc	624
Tyr Glu Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Asp Cys Gln Ala	
195 200 205	
tgg gat tct cag agc cca cat gct cat gga tac atc cct gcc aaa ttt	672
Trp Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ala Lys Phe	
210 215 220	
cca agc aag aac ctg aag atg aat tat tgc cac aac cct gac ggg gag	720
Pro Ser Lys Asn Leu Lys Met Asn Tyr Cys His Asn Pro Asp Gly Glu	
225 230 235 240	
cca agg ccc tgg tgc ttc aca aca gac ccc acc aaa cgc tgg gaa tac	768
Pro Arg Pro Trp Cys Phe Thr Thr Asp Pro Thr Lys Arg Trp Glu Tyr	
245 250 255	
tgt gac atc ccc cgc tgc aca aca ccc ccg ccc cca ccc agc cca acc	816
Cys Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Pro Pro Ser Pro Thr	
260 265 270	
tac caa tgt ctg aaa gga aga ggt gaa aat tac cga ggg acc gtg tct	864
Tyr Gln Cys Leu Lys Gly Arg Gly Glu Asn Tyr Arg Gly Thr Val Ser	

275	280	285	
gtc acc gtg tct ggg aaa acc tgt cag cgc tgg agt gag caa acc cct			912
Val Thr Val Ser Gly Lys Thr Cys Gln Arg Trp Ser Glu Gln Thr Pro			
290	295	300	
cat agg cac aac agg aca cca gaa aat ttc ccc tgc aaa aat ctg gaa			960
His Arg His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Glu			
305	310	315	320
gag aac tac tgc cgg aac cca gat gga gaa act gct ccc tgg tgc tat			1008
Glu Asn Tyr Cys Arg Asn Pro Asp Gly Glu Thr Ala Pro Trp Cys Tyr			
325	330	335	
acc act gac agc cag ctg agg tgg gag tac tgt gag att cca tcc tgc			1056
Thr Thr Asp Ser Gln Leu Arg Trp Glu Tyr Cys Glu Ile Pro Ser Cys			
340	345	350	
gag tcc tca gca tca cca gac cag tca gat tcc tca gtt cca cca gag			1104
Glu Ser Ser Ala Ser Pro Asp Gln Ser Asp Ser Ser Val Pro Pro Glu			
355	360	365	
gag caa aca cct gtg gtc cag gaa tgc tac cag agc gat ggg cag agc			1152
Glu Gln Thr Pro Val Val Gln Glu Cys Tyr Gln Ser Asp Gly Gln Ser			
370	375	380	
tat cgg ggt aca tgc tcc act acc atc aca ggg aag aag tgc cag tcc			1200
Tyr Arg Gly Thr Ser Ser Thr Thr Ile Thr Gly Lys Lys Cys Gln Ser			
385	390	395	400
tgg gca gct atg ttt cca cac agg cat tgc aag acc cca gag aac ttc			1248
Trp Ala Ala Met Phe Pro His Arg His Ser Lys Thr Pro Glu Asn Phe			
405	410	415	
cca gat gct ggc ttg gag atg aac tac tgc agg aac ccg gat ggt gac			1296
Pro Asp Ala Gly Leu Glu Met Asn Tyr Cys Arg Asn Pro Asp Gly Asp			
420	425	430	
aag ggc cct tgg tgc tac acc act gac ccg agc gtc agg tgg gaa tac			1344
Lys Gly Pro Trp Cys Tyr Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr			
435	440	445	
tgc aac ctg aag cgg tgc tca gag aca gga ggg aat tca gac tac aag			1392
Cys Asn Leu Lys Arg Cys Ser Glu Thr Gly Gly Asn Ser Asp Tyr Lys			
450	455	460	
gac gac gat gac aag taa taa c			1414
Asp Asp Asp Asp Lys * *			
465			

<210> 12
 <211> 469
 <212> PRT
 <213> Mus musculus

<400> 12
 Met Asp His Lys Glu Val Ile Leu Leu Phe Leu Leu Leu Leu Lys Pro
 1 5 10 15
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 20 25 30
 Leu Phe Ser Leu Thr Lys Lys Gln Leu Ala Ala Gly Gly Val Ser Asp
 35 40 45
 Cys Leu Ala Lys Cys Glu Gly Glu Thr Asp Phe Val Cys Arg Ser Phe
 50 55 60
 Gln Tyr His Ser Lys Glu Gln Gln Cys Val Ile Met Ala Glu Asn Ser
 65 70 75 80
 Lys Thr Ser Ser Ile Ile Arg Met Arg Asp Val Ile Leu Phe Glu Lys
 85 90 95
 Arg Val Tyr Leu Ser Glu Cys Lys Thr Gly Ile Gly Asn Gly Tyr Arg
 100 105 110
 Gly Thr Met Ser Arg Thr Lys Ser Gly Val Ala Cys Gln Lys Trp Gly
 115 120 125
 Ala Thr Phe Pro His Val Pro Asn Tyr Ser Pro Ser Thr His Pro Asn
 130 135 140
 Glu Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Glu Gln
 145 150 155 160
 Gly Pro Trp Cys Tyr Thr Thr Asp Pro Asp Lys Arg Tyr Asp Tyr Cys
 165 170 175
 Asn Ile Pro Glu Cys Glu Glu Glu Cys Met Tyr Cys Ser Gly Glu Lys
 180 185 190
 Tyr Glu Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Asp Cys Gln Ala
 195 200 205
 Trp Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ala Lys Phe
 210 215 220
 Pro Ser Lys Asn Leu Lys Met Asn Tyr Cys His Asn Pro Asp Gly Glu
 225 230 235 240
 Pro Arg Pro Trp Cys Phe Thr Thr Asp Pro Thr Lys Arg Trp Glu Tyr
 245 250 255
 Cys Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Pro Ser Pro Thr
 260 265 270
 Tyr Gln Cys Leu Lys Gly Arg Gly Glu Asn Tyr Arg Gly Thr Val Ser
 275 280 285
 Val Thr Val Ser Gly Lys Thr Cys Gln Arg Trp Ser Glu Gln Thr Pro
 290 295 300
 His Arg His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Glu
 305 310 315 320
 Glu Asn Tyr Cys Arg Asn Pro Asp Gly Glu Thr Ala Pro Trp Cys Tyr
 325 330 335
 Thr Thr Asp Ser Gln Leu Arg Trp Glu Tyr Cys Glu Ile Pro Ser Cys
 340 345 350
 Glu Ser Ser Ala Ser Pro Asp Gln Ser Asp Ser Ser Val Pro Pro Glu
 355 360 365
 Glu Gln Thr Pro Val Val Gln Glu Cys Tyr Gln Ser Asp Gly Gln Ser
 370 375 380
 Tyr Arg Gly Thr Ser Ser Thr Thr Ile Thr Gly Lys Lys Cys Gln Ser
 385 390 395 400
 Trp Ala Ala Met Phe Pro His Arg His Ser Lys Thr Pro Glu Asn Phe
 405 410 415
 Pro Asp Ala Gly Leu Glu Met Asn Tyr Cys Arg Asn Pro Asp Gly Asp
 420 425 430

Lys Gly Pro Trp Cys Tyr Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr
 435 440 445
 Cys Asn Leu Lys Arg Cys Ser Glu Thr Gly Gly Asn Ser Asp Tyr Lys
 450 455 460
 Asp Asp Asp Asp Lys
 465

<210> 13
 <211> 661
 <212> DNA
 <213> Mus musculus

<220>
 <221> CDS
 <222> (1)...(661)

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 Met Asp His Lys Glu Val Ile Leu Leu Phe Leu Leu Leu Leu Lys Pro
 1 5 10 15
 gga caa ggg gac tcg cta gat ctt gac tac aag gac gac gat gac aag 96
 Gly Gln Gly Asp Ser Leu Asp Leu Asp Tyr Lys Asp Asp Asp Asp Lys
 20 25 30
 ctt gct cat act cat cag gac ttt cag cca gtg ctc cac ctg gtg gca 144
 Leu Ala His Thr His Gln Asp Phe Gln Pro Val Leu His Leu Val Ala
 35 40 45
 ctg aac acc ccc ctg tct gga ggc atg cgt ggt atc cgt gga gca gat 192
 Leu Asn Thr Pro Leu Ser Gly Gly Met Arg Gly Ile Arg Gly Ala Asp
 50 55 60
 ttc cag tgc ttc cag caa gcc cga gcc gtg ggg ctg tcg ggc acc ttc 240
 Phe Gln Cys Phe Gln Gln Ala Arg Ala Val Gly Leu Ser Gly Thr Phe
 65 70 75 80
 cgg gct ttc ctg tcc tct agg ctg cag gat ctc tat agc atc gtg cgc 288
 Arg Ala Phe Leu Ser Ser Arg Leu Gln Asp Leu Tyr Ser Ile Val Arg
 85 90 95
 cgt gct gac cgg ggg tct gtg ccc atc gtc aac ctg aag gac gag gtg 336
 Arg Ala Asp Arg Gly Ser Val Pro Ile Val Asn Leu Lys Asp Glu Val
 100 105 110
 cta tct ccc agc tgg gac tcc ctg ttt tct ggc tcc cag ggt caa gtg 384
 Leu Ser Pro Ser Trp Asp Ser Leu Phe Ser Gly Ser Gln Gly Gln Val
 115 120 125
 caa ccc ggg gcc cgc atc ttt tct ttt gac ggc aga gat gtc ctg aga 432
 Gln Pro Gly Ala Arg Ile Phe Ser Phe Asp Gly Arg Asp Val Leu Arg
 130 135 140
 cac cca gcc tgg ccg cag aag agc gta tgg cac ggc tcg gac ccc agt 480
 His Pro Ala Trp Pro Gln Lys Ser Val Trp His Gly Ser Asp Pro Ser

145 150 155 160
 ggg cgg agg ctg atg gag agt tac tgt gag aca tgg cga act gaa act 528
 Gly Arg Arg Leu Met Glu Ser Tyr Cys Glu Thr Trp Arg Thr Glu Thr
 165 170 175
 act ggg gct aca ggt cag gcc tcc tcc ctg ctg tca ggc agg ctc ctg 576
 Thr Gly Ala Thr Gly Gln Ala Ser Ser Leu Leu Ser Gly Arg Leu Leu
 180 185 190
 gaa cag aaa gct gcg agc tgc cac aac agc tac atc gtc ctg tgc att 624
 Glu Gln Lys Ala Ala Ser Cys His Asn Ser Tyr Ile Val Leu Cys Ile
 195 200 205
 gag aat agc ttc atg acc tct ttc tcc aaa taa taa c 661
 Glu Asn Ser Phe Met Thr Ser Phe Ser Lys * *
 210 215

<210> 14
 <211> 218
 <212> PRT
 <213> Mus musculus

<400> 14
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 20 25 30
 Leu Ala His Thr His Gln Asp Phe Gln Pro Val Leu His Leu Val Ala
 35 40 45
 Leu Asn Thr Pro Leu Ser Gly Gly Met Arg Gly Ile Arg Gly Ala Asp
 50 55 60
 Phe Gln Cys Phe Gln Gln Ala Arg Ala Val Gly Leu Ser Gly Thr Phe
 65 70 75 80
 Arg Ala Phe Leu Ser Ser Arg Leu Gln Asp Leu Tyr Ser Ile Val Arg
 85 90 95
 Arg Ala Asp Arg Gly Ser Val Pro Ile Val Asn Leu Lys Asp Glu Val
 100 105 110
 Leu Ser Pro Ser Trp Asp Ser Leu Phe Ser Gly Ser Gln Gly Gln Val
 115 120 125
 Gln Pro Gly Ala Arg Ile Phe Ser Phe Asp Gly Arg Asp Val Leu Arg
 130 135 140
 His Pro Ala Trp Pro Gln Lys Ser Val Trp His Gly Ser Asp Pro Ser
 145 150 155 160
 Gly Arg Arg Leu Met Glu Ser Tyr Cys Glu Thr Trp Arg Thr Glu Thr
 165 170 175
 Thr Gly Ala Thr Gly Gln Ala Ser Ser Leu Leu Ser Gly Arg Leu Leu
 180 185 190
 Glu Gln Lys Ala Ala Ser Cys His Asn Ser Tyr Ile Val Leu Cys Ile
 195 200 205
 Glu Asn Ser Phe Met Thr Ser Phe Ser Lys
 210 215

<210> 15

<211> 1747
 <212> DNA
 <213> Mus musculus

<220>
 <221> CDS
 <222> (1)...(1747)

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  1              5              10              15

gga caa ggg gac tcg ctg gat ggc tac ata agc aca caa ggg gct tca      96
Gly Gln Gly Asp Ser Leu Asp Gly Tyr Ile Ser Thr Gln Gly Ala Ser
      20              25              30

ctg ttc agt ctc acc aag aag cag ctc gca gca gga ggt gtc tcg gac      144
Leu Phe Ser Leu Thr Lys Lys Gln Leu Ala Ala Gly Gly Val Ser Asp
      35              40              45

tgt ttg gcc aaa tgt gaa ggg gaa aca gac ttt gtc tgc agg tca ttc      192
Cys Leu Ala Lys Cys Glu Gly Glu Thr Asp Phe Val Cys Arg Ser Phe
      50              55              60

cag tac cac agc aaa gag cag caa tgc gtg atc atg gcg gag aac agc      240
Gln Tyr His Ser Lys Glu Gln Gln Cys Val Ile Met Ala Glu Asn Ser
      65              70              75              80

aag act tcc tcc atc atc cgg atg aga gac gtc atc tta ttc gaa aag      288
Lys Thr Ser Ser Ile Ile Arg Met Arg Asp Val Ile Leu Phe Glu Lys
      85              90              95

aga gtg tat ctg tca gaa tgt aag acc ggc atc ggc aac ggc tac aga      336
Arg Val Tyr Leu Ser Glu Cys Lys Thr Gly Ile Gly Asn Gly Tyr Arg
      100              105              110

gga acc atg tcc agg aca aag agt ggt gtt gcc tgt caa aag tgg ggt      384
Gly Thr Met Ser Arg Thr Lys Ser Gly Val Ala Cys Gln Lys Trp Gly
      115              120              125

gcc acg ttc ccc cac gta ccc aac tac tct ccc agt aca cat ccc aat      432
Ala Thr Phe Pro His Val Pro Asn Tyr Ser Pro Ser Thr His Pro Asn
      130              135              140

gag gga cta gaa gag aac tac tgt agg aac cca gac aat gat gaa caa      480
Glu Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Glu Gln
      145              150              155              160

ggg cct tgg tgc tac act aca gat ccg gac aag aga tat gac tac tgc      528
Gly Pro Trp Cys Tyr Thr Thr Asp Pro Asp Lys Arg Tyr Asp Tyr Cys
      165              170              175

aac att cct gaa tgt gaa gag gaa tgc atg tac tgc agt gga gaa aag      576
Asn Ile Pro Glu Cys Glu Glu Glu Cys Met Tyr Cys Ser Gly Glu Lys

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180	185	190	
tat gag ggc aaa atc tcc aag acc atg tct gga ctt gac tgc cag gcc			624
Tyr Glu Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Asp Cys Gln Ala			
195	200	205	
tgg gat tct cag agc cca cat gct cat gga tac atc cct gcc aaa ttt			672
Trp Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ala Lys Phe			
210	215	220	
cca agc aag aac ctg aag atg aat tat tgc cac aac cct gac ggg gag			720
Pro Ser Lys Asn Leu Lys Met Asn Tyr Cys His Asn Pro Asp Gly Glu			
225	230	235	240
cca agg ccc tgg tgc ttc aca aca gac ccc acc aaa cgc tgg gaa tac			768
Pro Arg Pro Trp Cys Phe Thr Thr Asp Pro Thr Lys Arg Trp Glu Tyr			
	245	250	255
tgt gac atc ccc cgc tgc aca aca ccc ccg ccc cca ccc agc cca acc			816
Cys Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Pro Pro Ser Pro Thr			
	260	265	270
tac caa tgt ctg aaa gga aga ggt gaa aat tac cga ggg acc gtg tct			864
Tyr Gln Cys Leu Lys Gly Arg Gly Glu Asn Tyr Arg Gly Thr Val Ser			
	275	280	285
gtc acc gtg tct ggg aaa acc tgt cag cgc tgg agt gag caa acc cct			912
Val Thr Val Ser Gly Lys Thr Cys Gln Arg Trp Ser Glu Gln Thr Pro			
	290	295	300
cat agg cac aac agg aca cca gaa aat ttc ccc tgc aaa aat ctg gaa			960
His Arg His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Glu			
	305	310	315
gag aac tac tgc cgg aac cca gat gga gaa act gct ccc tgg tgc tat			1008
Glu Asn Tyr Cys Arg Asn Pro Asp Gly Glu Thr Ala Pro Trp Cys Tyr			
	325	330	335
acc act gac agc cag ctg agg tgg gag tac tgt gag att cca tcc tgc			1056
Thr Thr Asp Ser Gln Leu Arg Trp Glu Tyr Cys Glu Ile Pro Ser Cys			
	340	345	350
gag tcc tca gca tca cca gac cag tca gat tcc tca gtt cca cca gag			1104
Glu Ser Ser Ala Ser Pro Asp Gln Ser Asp Ser Ser Val Pro Pro Glu			
	355	360	365
gag caa aca cct gtg gga ggg aat tgc ggc ggt gga tca ggt ggc gga			1152
Glu Gln Thr Pro Val Gly Gly Asn Cys Gly Gly Gly Ser Gly Gly Gly			
	370	375	380
gat ctt gac tac aag gac gac gat gac aag ctt gct cat act cat cag			1200
Asp Leu Asp Tyr Lys Asp Asp Asp Asp Lys Leu Ala His Thr His Gln			
	385	390	395
gac ttt cag cca gtg ctc cac ctg gtg gca ctg aac acc ccc ctg tct			1248

Asp	Phe	Gln	Pro	Val	Leu	His	Leu	Val	Ala	Leu	Asn	Thr	Pro	Leu	Ser		
				405					410					415			
gga	ggc	atg	cgt	ggg	atc	cgt	gga	gca	gat	ttc	cag	tgc	ttc	cag	caa	1296	
Gly	Gly	Met	Arg	Gly	Ile	Arg	Gly	Ala	Asp	Phe	Gln	Cys	Phe	Gln	Gln		
			420					425					430				
gcc	cga	gcc	gtg	ggg	ctg	tcg	ggc	acc	ttc	cgg	gct	ttc	ctg	tcc	tct	1344	
Ala	Arg	Ala	Val	Gly	Leu	Ser	Gly	Thr	Phe	Arg	Ala	Phe	Leu	Ser	Ser		
		435					440					445					
agg	ctg	cag	gat	ctc	tat	agc	atc	gtg	cgc	cgt	gct	gac	cgg	ggg	tct	1392	
Arg	Leu	Gln	Asp	Leu	Tyr	Ser	Ile	Val	Arg	Arg	Ala	Asp	Arg	Gly	Ser		
	450					455					460						
gtg	ccc	atc	gtc	aac	ctg	aag	gac	gag	gtg	cta	tct	ccc	agc	tgg	gac	1440	
Val	Pro	Ile	Val	Asn	Leu	Lys	Asp	Glu	Val	Leu	Ser	Pro	Ser	Trp	Asp		
465					470					475					480		
tcc	ctg	ttt	tct	ggc	tcc	cag	ggg	caa	gtg	caa	ccc	ggg	gcc	cgc	atc	1488	
Ser	Leu	Phe	Ser	Gly	Ser	Gln	Gly	Gln	Val	Gln	Pro	Gly	Ala	Arg	Ile		
				485				490					495				
ttt	tct	ttt	gac	ggc	aga	gat	gtc	ctg	aga	cac	cca	gcc	tgg	ccg	cag	1536	
Phe	Ser	Phe	Asp	Gly	Arg	Asp	Val	Leu	Arg	His	Pro	Ala	Trp	Pro	Gln		
			500					505					510				
aag	agc	gta	tgg	cac	ggc	tcg	gac	ccc	agt	ggg	cgg	agg	ctg	atg	gag	1584	
Lys	Ser	Val	Trp	His	Gly	Ser	Asp	Pro	Ser	Gly	Arg	Arg	Leu	Met	Glu		
		515					520					525					
agt	tac	tgt	gag	aca	tgg	cga	act	gaa	act	act	ggg	gct	aca	ggg	cag	1632	
Ser	Tyr	Cys	Glu	Thr	Trp	Arg	Thr	Glu	Thr	Thr	Gly	Ala	Thr	Gly	Gln		
	530					535					540						
gcc	tcc	tcc	ctg	ctg	tca	ggc	agg	ctc	ctg	gaa	cag	aaa	gct	gcg	agc	1680	
Ala	Ser	Ser	Leu	Leu	Ser	Gly	Arg	Leu	Leu	Glu	Gln	Lys	Ala	Ala	Ser		
545					550					555					560		
tgc	cac	aac	agc	tac	atc	gtc	ctg	tgc	att	gag	aat	agc	ttc	atg	acc	1728	
Cys	His	Asn	Ser	Tyr	Ile	Val	Leu	Cys	Ile	Glu	Asn	Ser	Phe	Met	Thr		
				565				570						575			
tct	ttc	tcc	aaa	taa	taa	c										1747	
Ser	Phe	Ser	Lys	*	*												
			580														

<210> 16
 <211> 580
 <212> PRT
 <213> Mus musculus

<400> 16
 Met Asp His Lys Glu Val Ile Leu Leu Phe Leu Leu Leu Lys Pro

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 35 40 45
 Cys Leu Ala Lys Cys Glu Gly Glu Thr Asp Phe Val Cys Arg Ser Phe
 50 55 60
 Gln Tyr His Ser Lys Glu Gln Gln Cys Val Ile Met Ala Glu Asn Ser
 65 70 75 80
 Lys Thr Ser Ser Ile Ile Arg Met Arg Asp Val Ile Leu Phe Glu Lys
 85 90 95
 Arg Val Tyr Leu Ser Glu Cys Lys Thr Gly Ile Gly Asn Gly Tyr Arg
 100 105 110
 Gly Thr Met Ser Arg Thr Lys Ser Gly Val Ala Cys Gln Lys Trp Gly
 115 120 125
 Ala Thr Phe Pro His Val Pro Asn Tyr Ser Pro Ser Thr His Pro Asn
 130 135 140
 Glu Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Glu Gln
 145 150 155 160
 Gly Pro Trp Cys Tyr Thr Thr Asp Pro Asp Lys Arg Tyr Asp Tyr Cys
 165 170 175
 Asn Ile Pro Glu Cys Glu Glu Glu Cys Met Tyr Cys Ser Gly Glu Lys
 180 185 190
 Tyr Glu Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Asp Cys Gln Ala
 195 200 205
 Trp Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ala Lys Phe
 210 215 220
 Pro Ser Lys Asn Leu Lys Met Asn Tyr Cys His Asn Pro Asp Gly Glu
 225 230 235 240
 Pro Arg Pro Trp Cys Phe Thr Thr Asp Pro Thr Lys Arg Trp Glu Tyr
 245 250 255
 Cys Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Pro Ser Pro Thr
 260 265 270
 Tyr Gln Cys Leu Lys Gly Arg Gly Glu Asn Tyr Arg Gly Thr Val Ser
 275 280 285
 Val Thr Val Ser Gly Lys Thr Cys Gln Arg Trp Ser Glu Gln Thr Pro
 290 295 300
 His Arg His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Glu
 305 310 315 320
 Glu Asn Tyr Cys Arg Asn Pro Asp Gly Glu Thr Ala Pro Trp Cys Tyr
 325 330 335
 Thr Thr Asp Ser Gln Leu Arg Trp Glu Tyr Cys Glu Ile Pro Ser Cys
 340 345 350
 Glu Ser Ser Ala Ser Pro Asp Gln Ser Asp Ser Ser Val Pro Pro Glu
 355 360 365
 Glu Gln Thr Pro Val Gly Gly Asn Cys Gly Gly Gly Ser Gly Gly Gly
 370 375 380
 Asp Leu Asp Tyr Lys Asp Asp Asp Asp Lys Leu Ala His Thr His Gln
 385 390 395 400
 Asp Phe Gln Pro Val Leu His Leu Val Ala Leu Asn Thr Pro Leu Ser
 405 410 415
 Gly Gly Met Arg Gly Ile Arg Gly Ala Asp Phe Gln Cys Phe Gln Gln
 420 425 430
 Ala Arg Ala Val Gly Leu Ser Gly Thr Phe Arg Ala Phe Leu Ser Ser
 435 440 445

Arg Leu Gln Asp Leu Tyr Ser Ile Val Arg Arg Ala Asp Arg Gly Ser
 450 455 460
 Val Pro Ile Val Asn Leu Lys Asp Glu Val Leu Ser Pro Ser Trp Asp
 465 470 475 480
 Ser Leu Phe Ser Gly Ser Gln Gly Gln Val Gln Pro Gly Ala Arg Ile
 485 490 495
 Phe Ser Phe Asp Gly Arg Asp Val Leu Arg His Pro Ala Trp Pro Gln
 500 505 510
 Lys Ser Val Trp His Gly Ser Asp Pro Ser Gly Arg Arg Leu Met Glu
 515 520 525
 Ser Tyr Cys Glu Thr Trp Arg Thr Glu Thr Thr Gly Ala Thr Gly Gln
 530 535 540
 Ala Ser Ser Leu Leu Ser Gly Arg Leu Leu Glu Gln Lys Ala Ala Ser
 545 550 555 560
 Cys His Asn Ser Tyr Ile Val Leu Cys Ile Glu Asn Ser Phe Met Thr
 565 570 575
 Ser Phe Ser Lys
 580

<210> 17
 <211> 549
 <212> DNA
 <213> Homo sapiens

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 gggctggcgg gcaccttccg cgccttcctg tcctcgccgc tgcaggacct gtacagcatc 180
 gtgcgccgtg ccgaccgcgc agccgtgccc atcgtaacc tcaaggacga gctgctgttt 240
 cccagctggg aggtctctgtt ctcaggctct gaggggccgc tgaagcccgg ggcacgcac 300
 ttctcctttg acggcaagga cgtcctgagg caccaccct ggccccagaa gagcgtgtgg 360
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/24950

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A01N 63/00, 43/04; C12N 15/00; C07H 21/02.

US CL : 424/93.1; 435/320.1; 514/44; 536/23.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/93.1; 435/320.1; 514/44; 536/23.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	US 5,792,845 A (O'REILLY et al.) 11 August 1998 (11.08.98), col. 4, lines 32-68, col. 5, lines 1-2, 51-68, col. 6, lines 1-8.	1-30, 33
Y	WO 97/23500 A1 (THE CHILDREN'S MEDICAL CENTER CORPORATION) 03 July 1997 (03.07.97), page 41, lines 3-33, page 42, lines 1-27.	4
X,P ----- Y,P	WO 98/49321 A2 (RHONE-POULENC RORER) 05 November 1998 (05.11.98), page 44, 6-11, 25-33, page 45, lines 12-13, 29-35.	1, 5, 18, 20, 31 ----- 2-4, 6-17, 19, 21-30, 32, 33

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

04 FEBRUARY 1999

Date of mailing of the international search report

08 MAR 1999

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

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SHIN-LIN CHEN

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Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/24950

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97/15666 A (THE CHILDREN'S MEDICAL CENTER CORPORATION) 01 May 1997 (01.05.97), page 20, lines 16-35, page 21, page 22, lines 1-16. page 59, lines 5-35, page 60, page 61, 1-6.	1-30, 33
Y	TANAKA, T. et al. Retroviral and adenoviral mediated transduction of angiostatin cDNA inhibits angiogenesis and tumor growth. Proceedings of the American Association for Cancer Research. March 1997 (03.97). Vol 38. page 264.	1-33
Y	WO 96/35774 A2 (THE CHILDREN'S MEDICAL CENTER CORPORATION) 14 November 1996 (14.11.96), page lines 33-36, pages 22-25, page 26, lines 1-33. pages 144-148.	1-30, 33
Y	WO 97/41824 A2(ABBOTT LABORATORIES) 13 November 1997 (13.11.97), page 5, lines 13-38, page 6, 1-18, page 60, lines 15-38, pages 61-62, page 63, lines 1-33.	1-30, 33
Y	WO 95/29242 A1 (THE CHILDREN'S MEDICAL CENTER CORPORATION) 02 November 1995 (02.11.95), page 21, lines 19-35, pages 22-27, page 28, lines 1-4. page 87, lines 4-35, page 88, page 89, lines 1-14.	1-30, 33
Y	O'REILLY, et al. Angiostatin induces and sustains dormancy of human primary tumors in mice. Nature Medicine, June 1996 (06.96), Vol. 2, No. 6, pages 689-692, especially pages 689-690.	1-30, 33
Y	O'REILLY, et al. Endostatin: An Endogenous Inhibitor of Angiogenesis and Tumor Growth. Cell, 24 January 1997 (24.01.97), Vol. 88, pages 277-285, especially pages 279-280, 282.	1-30, 33

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/24950

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS, STN, WPIDS, MEDLINE, CAPLUS, BIOSIS, EMBASE

search terms: angiostatin, plasminogen, endostatin, collagen(w) XVIII, inhibit?(5a)tumor(5a)growth, tumor(5a)regress?, diabet?(p)retinopathy, plasmid, viral(5a) vector.

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